

**Table S-1: Summary of Reactive Intermediates Utilized in Multi-Stage Syntheses during 2001
(Reported in Organic Process R&D)**

| Drug Substance | No. of Synthetic stages ^a | Stage that Reactive Intermediate Introduced | Nature of Reactive intermediate | Reference |
|----------------|--------------------------------------|---|---|--------------|
| RG 12525 | 5 | 2 4 5 | Alkyl halide, Quinone Alkyl halide Azide | ¹ |
| Darusentan | 5 | 1 2 5 | Alkyl halide Epoxide, MTS ^b Substituted pyrimidine | ² |
| Tenidap | 4 | 2 3 4 | Isocyanate Acid halide Michael acceptor (x2) | ³ |
| Sulamserod | 11 | 1 2 3 4 5 6 7 8 9 10 11 | NCS ^c Alkyl halide Aromatic nitro Aromatic amine NCS ^c Alkyl halide Aromatic amine, Aromatic aldehyde Aromatic amine/Michael acceptor Aromatic amine, ISA ^d Aromatic amine Aromatic amine, Alkyl halide ^e | ⁴ |
| CP-060S | 5 | 1 3 4 | Aromatic aldehyde Acid halide Alkyl halide | ⁵ |
| PNU-142731A | 5 | 1 2 3 4 5 | Substituted pyrimidine Substituted pyrimidine, Alkyl halide Substituted pyrimidine Substituted pyrimidine, Alkyl halide Substituted pyrimidine, Alkyl halide | ⁶ |
| Aminoindan | 2 | 1 2 | Hydroxylamine Oxime | ⁷ |
| Celiprolol | 4 | 1 2 3 | Aromatic amine, Acid halide Acid halide Epoxide, Alkyl halide | ⁸ |
| CI-972 | 5 | 1 2 | Acrylate, Aromatic aldehyde Acrylate | ⁹ |

¹ Bridge, A.W.; Jones, R.H.; Kabir, H.; Kee, A.A.; et al., *Org. Proc. R&D.* **2001**, 5, 9-15.

² Jansen, R.; Knopp, M.; Amberg, W.; Bernard, H.; et al., *Ibid*, **2001**, 5, 16-22.

³ Kumar, R.R.; Goud, P.S.; Raju, S.; Sailaja, M.; et al., *Ibid*, **2001**, 5, 61-64.

⁴ Kowalczyk, B.A.; Robinson, J.; Gardner, J.O.; *ibid*, **2001**, 5, 116-121.

⁵ Kasto, T.; Ozaki, T.; Tsuzuki, K.; Ohi, N.; *ibid*, **2011**, 5, 122-126.

⁶ Bundy, G.L.; Bannitt, L.S.; Dobrowolski, P.J.; Palmer, J.R.; et al., *ibid*, **2001**, 5, 144-151.

⁷ Roche, D.; Sans, D.; Grgis, M.J.; Prasad, K.; et al., *ibid*, **2001**, 5, 167-175.

⁸ Joshi, R.A.; Gurjar, M.K.; Tripathy, N.K.; *ibid*, **2001**, 5, 176-178.

⁹ De Jong, R.L.; Davidson, J.G.; Dozeman, G.J.; Fiore, P.J.; et al., R.E.; *ibid*, **2001**, 5, 216-225.

| | | | | |
|--------------------------------|---|----------------------------|---|---------------|
| | | 3 4 5 | Aromatic nitro Aromatic nitro, Aromatic aldehyde Aromatic amine, Alkyl halide ^e | |
| CI-1020 | 5 | 1 2 3 5 | Aromatic aldehyde Michael acceptor MTS ^b Michael acceptor | ¹⁰ |
| Eniluracil | 2 | 1 2 | Substituted uracil , TMSA ^f Substituted uracil (x2), Michael acceptor (x2) | ¹¹ |
| KF31327 | 8 | 3 4 5 6 7 8 | Aromatic amine, Formamide Aromatic nitro Aromatic nitro Aromatic nitro, Acid halide Aromatic nitro Aromatic amine, Carbon disulfide | ¹² |
| R116010 | 4 | 1 2 3 4 | Acid halide MSC ^g Aromatic amine, Alkyl halide, Carbon disulfide Aromatic amine | ¹³ |
| Idoxifene | 5 | 1 2 3 4 | Acid halide Alkyl halide, Alkyl halide Alkyl halide, Alkyl halide Alkyl halide, Alkyl halide ^e | ¹⁴ |
| Lescol | 9 | 1 2 3 6 | Alkyl halide Diazonium Alkyl halide Michael addition, Alkyl aldehyde | ¹⁵ |
| Bidisomide | 6 | 1 2 3 5 | Aromatic aldehyde Acid halide Alky halide Acid halide | ¹⁶ |
| PDE-IV inhibitor | 4 | 1 | Acid halide, Alkyl halide, Hydrazide | ¹⁷ |
| PDE-IV /TNF α inhibitor | 4 | 1 4 | Acid halide, Alkyl halide, Hydrazine Alkyl halide ^e | ¹⁸ |
| Sch 59884 | 5 | 1 2 3 4 5 | Alkyl halide/Aromatic nitro Aromatic nitro, Acid halide Aromatic nitro/Aryl phosphonate Aryl phosphonate, TSC ^h Aryl phosphonate | ¹⁹ |

¹⁰ Ellis, J.E.; Davis, E.M.; Dozeman, Lenoir, E.A.; *et al.*, *ibid*, **2001**, 5, 226-233.

¹¹ Cooke, J.W.B.; Bright, R.; Coleman, M.J.; Jenkins, K.P.; *ibid*, **2001**, 5, 383-386.

¹² Fujino, K.; Takami, H.; Atsumi, T.; Ogasa, T.; *et al.*, *ibid*, **2001**, 5, 426-433.

¹³ Aelterman, W.; Lang, Y.; Willemenssens, B.; Vervest, I.; *et al.*, *ibid*, **2001**, 5, 476-471.

¹⁴ Ace, K.W.; Armitage, M.A.; Bellingham, R.K.; Blackler, P.D.; *et al.*, *ibid*, **2001**, 5, 479-480.

¹⁵ Repič, O.; Prasad, K.; Lee, G.T.; *ibid*, **2001**, 5, 519-527.

¹⁶ Awasthi, A.K.; Paul, K.; *ibid*, **2001**, 5, 528-530.

¹⁷ Urban, F.J.; Anderson, B.G.; Orill, S.L.; Daniels, P.J.; *ibid*, **2001**, 5, 575-580.

¹⁸ Caron, S.; Vazquez, E.; *ibid*, **2001**, 5, 587-592.

¹⁹ Lee, G.M.; Eckert, J.; Gala, D.; Schwartz, M.; *et al.*, *ibid*, **2001**, 5, 622-629.

(a). Crystallization/salt formation is counted as a single stage, (b). MTS (methyl toxic acid), (c). NCS (*N*-chlorosuccinimide), (d). ISA (iodosulfonamide), (e). Reaction of HCL with alcohol solvent, (f). TMSA (trimethylsilyl acetylene), (g). MSC (mesityl chloride), (h). TSC (Tosyl chloride)

**Table S-2: Summary of Reactive Intermediates Utilized in Multi-Stage Syntheses during 2002
(Reported in Organic Process R&D)**

| Drug Substance | No. of Synthetic stages ^a | Stage that Reactive Intermediate Introduced | Nature of Reactive intermediate | Reference |
|---|--------------------------------------|---|---|---------------|
| 17 α -methyl-11 β -arylestradiol | 5 | 1 2 3 4 | Peroxide, Epoxide Epoxide, Alky halide Michael addition Acid halide | ²⁰ |
| DMP777 | 6 | 2 4 5 | Vinyl halide, Vinyl Alkyl halide ^b Isocyanate | ²¹ |
| Netilmicin | 3 | - | None identified | ²² |
| Sertraline | 2 | 1 | Methylhydroxylamine, Oxime | ²³ |
| Flosconazole | 3 | 3 | Peroxide | ²⁴ |
| Bosentan | 6 | 1 3 4 5 6 | Alkyl halide Substituted pyrimidine, Acid halide Substituted pyrimidine Substituted pyrimidine Substituted pyrimidine | ²⁵ |
| Travoprost | 12 | 1 2 3 5 6 12 | Vinyl butyrate MSC ^c Sulfonate ester Alkyl halide Alkyl halide Alkyl halide ^b | ²⁶ |
| LDL Receptor Upregulator | 4 | 3 | Alkyl halide ^b Alkyl halide | ²⁷ |
| DL-028A | 7 | 1 2 3 4 7 | Aromatic amine, carbon disulfide Alkyl halide Vinyl amine, vinyl Alkyl halide, NBS ^d Alkyl halide ^b | ²⁸ |
| BMS-232632 | 5 | 1 2 3 4 | Aromatic aldehyde Aromatic aldehyde Hydrazine, hydrazide, peroxide, epoxide Hydrazide | ²⁹ |
| ABT-518 | 5 | 2 | MSC ^c | ³⁰ |

²⁰ Larkin, J.P.; Wehrey, C.; Boffelli, P.; Lagraulet, H.; *et al.*, *ibid*, **2002**, 6, 20-27.

²¹ Storace, L.; Anzalone, L.; Conafalone, P.N.; Davis, W.P.; *et al.*, *ibid*, **2002**, 6, 54-63.

²² Nam, G.; Kim, S.H.; Kim, J-H.; Shin, J-H.; Jang, E-S.; *ibid*, **2002**, 6, 78-81.

²³ Vukics, K.; Fodor, T.; Fischer, J.; Fellegvári, I.; Lévai, S.; *ibid*, **2002**, 6, 82-85.

²⁴ Bentley, A.; Butters, M.; Green, S.P.; Learmonth, W.J.; *et al.*, *ibid*, **2002**, 6, 109-112.

²⁵ Harrington, P.J.; Khatri, H.N.; DeHoff, D.S.; Guin, M.R.; *et al.*, *ibid*, **2002**, 6, 120-124.

²⁶ Boulton, L.T.; Brick, D.; Fox, M.E.; Jackson, M.; *et al.*, *ibid*, **2002**, 6, 135-145.

²⁷ Ito, T.; Ikemoto, T.; Isogami, Y.; Wada, H.; *et al.*, *ibid*, **2002**, 6, 238-241.

²⁸ Chou, S-Y.; Yin, W-K.; Chung, Y-S.; Chang, L-S.; *et al.*, *ibid*, **2002**, 6, 273-278.

²⁹ Xu, Z.; Singh, J.; Schwinden, M.D.; Zheng, B.; *et al.*, *ibid*, **2002**, 6, 323-328.

³⁰ Chang, S-J.; Fernando, D.; Fickes, M.; Gupta, A.K.; *et al.*, *ibid*, **2002**, 6, 323-328.

| | | | | |
|-------------------------------------|---|---------------------------------|---|---------------|
| | | 3 4 5 | Michael addition, Hydroxylamine Hydroxylamine Hydroxylamine, Alkyl aldehyde | |
| NNC 26-1089 | 6 | 1 2 3 4 5 6 | Acid chloride, Hydrazine Hydrazide Hydrazide Hydrazide Hydrazide/Michael acceptor Hydrazide/Michael acceptor | ³¹ |
| Tolterodine | 5 | 2 | Alkyl aldehyde | ³² |
| GBR-12909 | 3 | 1 | Alkyl halide Alkyl halide, CTS ^e Alkyl halide | ³³ |
| BMS-270394 | 9 | 1 3 4 6 7 8 | Acid halide Alkyl halide, vinyl Vinyl Acid halide Aromatic amine, vinyl Vinyl | ³⁴ |
| SDZ 242-484 | 7 | 1 2 3 4 5 6 7 | Alkyl halide Alkyl halide alky halide Vinyl Vinyl, peroxide Hydroxylamine Hydroxamic acid | ³⁵ |
| 6 α -Fluoro-deoxycholic acid | 8 | 1 2 5 | Alkyl halide ^b NBS ^d Alkyl halide | ³⁶ |
| PNU-91325 | 6 | 2 3 4 5 6 | Vinyl, NBS ^d Epoxide, Aromatic aldehyde Aromatic aldehyde Michael acceptor, Acid halide Acid halide | ³⁷ |
| UK-357903 | 6 | 1 2 3 | Aromatic amine Aromatic amine, Diazonium, Acid halide, Alkyl halide Aromatic amine, Alkyl halide | ³⁸ |
| CP1975 | 3 | 1 2 3 | Alkyl halide Acid halide Alkyl phosphate | ³⁹ |
| BAY 43-9006 | 4 | 1 | Acid halide | ⁴⁰ |

³¹ Andersen, P.; Ankersen, M.; Jessen, C.U.; Lehman, S.V.; *ibid*, **2002**, 6, 367-373.

³² Botteghi, C.; Corrias, T.; Marchetti, M.; *et al.*, *ibid*, **2002**, 6, 379-383.

³³ Ironside, M.D.; Sugathapala, P.M.; Robertson, J.; Darey, M.C.P.; Zhang, J.; *ibid*, **2002**, 6, 621-627.

³⁴ Chidambaram, R.; Kant, J.; Zhu, J.; Lajeunesse, J.; *et al.*, *ibid*, **2002**, 6, 632-636.

³⁵ Koch, G.; Kottirisch, G.; Wietfeld, B.; Küsters, E.; *ibid*, **2002**, 6, 652-659.

³⁶ Königsberger, K.; Chen, G-P.; Vivelo, J.; Lee, G.; *et al.*, *ibid*, **2002**, 6, 665-669.

³⁷ Carpenter, D.E.; Imbordino, R.J.; Maloney, M.T.; Moeslein, J.A.; *et al.*, *ibid*, **2002**, 6, 721-728.

³⁸ Dale, D.J.; Draper, J.; Dunn, P.J.; Hughes, M.L.; *et al.*, *ibid*, **2002**, 6, 767-772.

³⁹ Prashad, M.; Amadio, J.C.; Ciszewski, L.; Lee, G.; *et al.*, *ibid*, **2002**, 6, 773-776.

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|--|--|---|----------------------------|--|
| | | 2 | Acid halide | |
| | | 3 | Aromatic amine | |
| | | 4 | Aromatic amine, Isocyanate | |

(a). Crystallization/salt formation is counted as a single stage, (b). Reaction of HCL with alcohol solvent, (c). MSC (methanesulfonyl chloride), (d). NBS (*N*-bromosuccinimide), (e). CTS (chloroethyltosic acid) formed via side reaction of tosic acid and alcohol

⁴⁰ Bankston, D.; Dumas, J.; Natero, R.; Riedl, B.; et al., *ibid*, **2002**, 6, 777-781.

**Table S-3: Summary of Reactive Intermediates Utilized in Multi-Stage Syntheses during 2003
(Reported in Organic Process R&D)**

| Drug Substance | No. of Synthetic stages ^a | Stage that Reactive Intermediate Introduced | Nature of Reactive intermediate | Reference |
|--|--------------------------------------|---|---|---------------|
| SB-207499 | 4 ^b | 2 4 | Acid halide Michael acceptor | ⁴¹ |
| ONO-2506 | 4 | 1 2 3 4 | Alkyl halide Alkyl halide Vinyl, peroxide Vinyl | ⁴² |
| Sampatrilat | 9 | 2 3 5 6 | Alkyl halide Alkyl halide, MPT ^c Alkyl halide/Vinyl Acrylate | ⁴³ |
| UK-370106 | 8 | 2 5 6 | Boronic acid Acid halide Alky halide | ⁴⁴ |
| OSU-6162 | 6 | 2 | Epoxide ^d | ⁴⁵ |
| PDE472 | 5 | 1 2 3 5 | Aromatic nitro/amine Aromatic nitro/amine Aromatic N-oxide Boronic acid | ⁴⁶ |
| HMR2934 | 6 | 1 2 3 | Acid halide (x2), Hydrazine Hydrazide Hydrazide, Tetrazene ^e | ⁴⁷ |
| FK366 | 7 | 1 2 3 5 6 7 | Aromatic amine, Acid halide Acid halide Alkyl halide Pyrimidine derivative Pyrimidine derivative, Alkyl halide Pyrimidine derivative | ⁴⁸ |
| 6-[2-(2,5-Dimethoxyphenyl)ethyl]-4-ethyl quinazoline | 3 | 1 | Aromatic aldehyde | ⁴⁹ |
| LB71350 | 6 | 1 4 | Azide Peroxide, Epoxide | ⁵⁰ |

⁴¹ Badham, N.F.; Chen, J-H.; Cummings, P.G.; Dell'Orco, P.C.; *et al.*, *ibid*, **2003**, 7, 101-108.

⁴² Hasegawa, T.; Kawanaka, Y.; Kasamatsu, E.; Iguchi, Y.; *et al.*, *ibid*, **2003**, 7, 168-171.

⁴³ Dunn, P.J.; Hughes, M.L.; Searle, P.M.; Wood, A.S.; *ibid*, **2003**, 7, 244-253.

⁴⁴ Ashcroft, C.P.; Challenger, S.; Derrick, A.M.; Storey, R.; *et al.*, *ibid*, **2003**, 7, 362-368.

⁴⁵ Lipton, M.F.; Mauragis, M.A.; Maloney, M.T.; Veley, M.F.; *et al.*, *ibid*, **2003**, 7, 385-392.

⁴⁶ Manley, P.W.; Acemoglu, M.; Marterer, W.; Pachinger, W.; *ibid*, **2003**, 7, 436-445.

⁴⁷ Watson, T.J.; Ayers, T.A.; Shah, N.; Wenstrup, D.; *et al.*, *ibid*, **2003**, 7, 521-532.

⁴⁸ Goto, S.; Tsuboi, H.; Kanoda, M.; Mukai, K.; *et al.*, *ibid*, **2003**, 7, 700-706.

⁴⁹ Königsbergerer, K.; Chen, G-P.; Wu, R.R.; Grgis, M.J.; *et al.*, *ibid*, **2003**, 7, 733-742.

⁵⁰ Lee, K.W.; Hwang, S.Y.; Kim, C.R.; Nam, D.H.; *et al.*, *ibid*, **2003**, 7, 839-845.

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|---|---|-----------------------|--|---------------|
| | | 5 6 | Epoxide Acid halide | |
| Pagoclone | 6 | 1 2 3 4 | Aromatic amine, Alkyl sulfate ^f Aromatic amine Acid halide Michael acceptor | ⁵¹ |
| LAF389 | 6 | 2 5 | Alkyl halide Alkyl halide | ⁵² |
| Elarofiban | 7 | 1 2 | Aryl aldehyde, Acid chloride Alkyl halide ^g | ⁵³ |
| 6-Ethoxy-4-oxo-1,4-dihydro-[1,5]naphthyridine-3-carboxylic acid benzylamide | 6 | 1 2 3 4 6 | Aromatic nitro Aromatic nitro Aromatic amine, Michael acceptor Michael acceptor Aromatic amine | ⁵⁴ |
| YM-087 | 5 | 1 2 3 5 | Aromatic nitro Aromatic amine Acid halide, Acid halide Alkyl halide ^g | ⁵⁵ |
| JNZ 092 | 5 | 2 3 4 5 | Acid chloride Acrylonitrile Alkyl aldehyde Alkyl halide | ⁵⁶ |
| T2288 | 3 | 1 2 | Acid halide Alkyl halide | ⁵⁷ |

(a). Crystallization/salt formation is counted as a single stage, (b). Reported from a key intermediate, which in turn was a 6-step synthesis, (c). MPT (2-methyl-1-propene tosylate, (d). *In situ* formation of per-acid by reaction of hydrogen peroxide with acid, (e). Bi-product of coupling of two hydrazide intermediates, (f). Reaction of H₂SO₄ with alcohol solvent, (g). Reaction of HCl with alcohol solvent.

⁵¹ Stuck, T.L.; Assink, B.K.; Bates, R.C.; Erdman, D.T.; *et al., ibid*, **2003**, 7, 851-855.

⁵² Xu, D.D.; Waykole, L.; Calienni, J.V.; Ciszewski, L.; *et al., ibid*, **2003**, 7, 856-865.

⁵³ Cohen, J.H.; Bos, M.E.; Cesco-Cancian, S.; Harris, B.D.; *et al., ibid*, **2003**, 7, 866-872.

⁵⁴ Beaudin, J.; Boiurassa, D.E.; Bowles, P.; Castaldi, M.J.; *et al., ibid*, **2003**, 7, 873-878.

⁵⁵ Tsunoda, T.; Yamazaki, A.; Iwamoto, H.; Sakamoto, S.; *ibid*, **2003**, 7, 883-887.

⁵⁶ Bänziger, M.; Küsters, E.; La Vecchia, L.; Marterer, W.; *et al., ibid*, **2003**, 7, 904-912.

⁵⁷ Guillaume, M.; Cuypers, J.; Vervest, I.; De Smaele, D.; *et al., ibid*, **2003**, 7, 939-941.

**Table S-4: Summary of Reactive Intermediates Utilized in Multi-Stage Syntheses during 2004
(Reported in Organic Process R&D)**

| Drug Substance | No. of Synthetic stages ^a | Stage that Reactive Intermediate Introduced | Nature of Reactive intermediate | Reference |
|---|--------------------------------------|---|--|---------------|
| Oseltamivir | 5 | 1 2 3 4 5 | Michael acceptor/Epoxide, Diazonium Michael acceptor /Diazonium Michael acceptor /Aziridine, Diazonium Michael acceptor /Diazonium Michael acceptor /Diazonium, Alkyl phosphate ^b | ⁵⁸ |
| Aminopyrazino-ne acetamide thrombin inhibitor | 7 ^c | 1 3 4 6 | Acid halide Alkyl halide, Alkyl sulfate ^d Acid halide Isocyanate | ⁵⁹ |
| CI-1034 | 7 | 1 2 3 4 6 | Aromatic aldehyde Aromatic aldehyde Aromatic aldehyde Aromatic aldehyde Boronic acid | ⁶⁰ |
| 4-Chloro-11β-arylestradiol | 7 | 1 2 3 5 6 | Peroxide ^e Peroxide, Alkyl halide Peroxide Michael acceptor, Acid halide Michael acceptor, Acid halide | ⁶¹ |
| Pantoprazole | 2 | 1 2 | Acid halide Peroxide ^e | ⁶² |
| SB-342219 | 3 | 2 3 | Acid halide Alkyl halide | ⁶³ |
| TKA731 | 9 | 1 3 4 6 8 | Acid halide Acid halide Alkyl halide Isocyanate Acid halide | ⁶⁴ |
| MIV-150 | 7 | 1 3 5 | Acid halide, Alkyl halide Vinyl, Brucine ^f Diazonium | ⁶⁵ |
| NNC 61-4655 | 4 | 1 2 | Alkyl aldehyde/Michael acceptor Michael acceptor | ⁶⁶ |
| Ro-28-2653 | 5 | 1 | ETS ^g | ⁶⁷ |

⁵⁸ Harrington, P.J.; Brown, J.D.; Foderano, T.; Hughes, R.C.; *ibid*, **2004**, 8, 86-91.

⁵⁹ Ashwood, M.S.; Alabaster, R.J.; Cottrell, I.F.; Cowden, C.J.; *et al.*, *ibid*, **2004**, 8, 192-200.

⁶⁰ Jacks, T.E.; Belmont, D.T.; Briggs, C.A.; Horne, N.M.; *et al.*, *ibid*, **2004**, 8, 201-202.

⁶¹ Prat, D.; Benedetti, F.; Girard, G.F.; Bouda, L.N.; *et al.*, *ibid*, **2004**, 8, 219-228.

⁶² Matthad, V.T.; Govindan, S.; Kolla, N.K.; Maddipatla, M.; *et al.*, *ibid*, **2004**, 8, 266-270.

⁶³ Bellingham, R.K.; Carey, J.S.; Hussain, N.; Morgan, D.O.; *et al.*, *ibid*, **2004**, 8, 279-282.

⁶⁴ Prashad, M.; Har, D.; Hu, B.; Kim, H-Y.; *et al.*, *ibid*, **2004**, 8, 330-340.

⁶⁵ Cai, S.; Dimitroff, M.; McKennon, T.; Reider, M.; *et al.*, *ibid*, **2004**, 8, 353-359.

⁶⁶ Deussen, H-J.; Jepesen, L.; Schärer, N.; Junager, F.; *et al.*, *ibid*, **2004**, 8, 363-371.

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|---------------------------------|----|--|--|---------------|
| | | 5 | Alkyl halide, Aromatic nitro (x2) | |
| CH8757 | 7 | 2 4 5 6 7 | Alkyl halide Acid halide Peroxide Oxime Oxime, Acid halide, Hydroxylamine, Hydroxamic acid/oxime, DMCC ^h | ⁶⁸ |
| β-3 Adrenergic Receptor Agonist | 8 | 1 2 3 4 | Aromatic amine Vinyl TSC ⁱ Sulfonate ester, Epoxide, Quinone methide ^j | ⁶⁹ |
| β-3 Adrenergic Receptor Agonist | 6 | 1 2 3 4 5 6 | Aromatic amine Acid halide Acid halide Acid halide Epoxide Hydroxylamine, Aromatic amine | ⁷⁰ |
| Sibenadet | 8 | 3 4 6 7 8 | Aromatic nitro, Alkyl halide ^k Aromatic amine, Isocyanate NBS ^l Aromatic amine, Diazonium Alkyl halide | ⁷¹ |
| Farnesyl transferase inhibitor | 11 | 1 2 3 5 6 7 8 9 10 11 | Aromatic nitro/acid chloride Aromatic nitro Aromatic nitro Aromatic amine Michael acceptor, Alkyl halide Michael acceptor Michael acceptor Michael acceptor Michael acceptor Michael acceptor | ⁷² |
| Cortisone acetate | 27 | 2 6 11 12 13 14 19 20 21 26 27 | Acid halide Michael acceptor Epoxide Epoxide Epoxide Epoxide Aromatic nitro (DNBS ^m) Epoxide Epoxide Hydrazine Hydrazide, Alkyl halide ^k , Michael | ⁷³ |

⁶⁷Daniewski, A.R.; Liu, W.; Okabe, M.; *ibid*, **2004**, 8, 411-414.

⁶⁸Frampton, G.A.; Hannah, D.R.; Henderson, N.; Katz, R.B.; *et al.*, *ibid*, **2004**, 8, 415-417.

⁶⁹Vanderplass, B.C.; DeVries, K.M.; Fox, D.E.; Raggon, J.W.; *et al.*, *ibid*, **2004**, 8, 583-586.

⁷⁰Vanderplass, B.C.; DeVries, K.M.; Fox, D.E.; Raggon, J.W.; *et al.*, *ibid*, **2004**, 8, 583-586.

⁷¹Giles, M.E.; Thomson, C.; Eyley, S.C.; Cole, A.J.; *et al.*, *ibid*, **2004**, 8, 628-642.

⁷²Anderson, B.M.; Couturier, M.; Cronin, B.; D'Occchio, M.; Ewing, M.D.; *et al.*, *ibid*, **2004**, 8, 643-650.

⁷³Pines, S.H.; *ibid*, **2004**, 8, 708-724.

| | | | acceptor | |
|---------------------------------------|-----------------|--|---|---------------|
| SB 273005 | 6 | 1 2 3 4 5 | Aromatic aldehyde Aromatic aldehyde, Alkyl halide ^k Aromatic aldehyde, Michael acceptor Alkyl sulfate ^d Aromatic aldehyde | ⁷⁴ |
| Cefmatilen | 4 | 1 2 3 4 | Oxime, Alkyl halide Oxime, Michael acceptor Oxime/Michael acceptor Oxime/Michael acceptor Oxime/Michael acceptor/Aromatic amine | ⁷⁵ |
| Sch 39166 | 4 | 1 2 | Alkyl halide TSC ⁱ | ⁷⁶ |
| Cardax | 2 ⁿ | 1 2 | Michael acceptor Michael acceptor (x2) | ⁷⁷ |
| MX-68 | 11 ^o | 1 8 10 11 | Aromatic amine Acid halide, Alkyl halide ^k Aromatic amine/alkyl halide Aromatic amine (x2) | ⁷⁸ |
| Fiduxosin | 11 | 2 3 4 6 7 8 10 11 | Aromatic aldehyde Aromatic aldehyde Michael acceptor Alkyl halide Alkyl halide ^k Alkyl halide Isocyanate Alkyl halide, Alkyl halide ^k | ⁷⁹ |
| Respiratory Syncytial Virus Inhibitor | 4 | 1 2 3 | Alkyl halide Acid halide Acid halide | ⁸⁰ |
| Cefotetan | 8 | 1 2 3 4 5 6 7 8 | Michael acceptor Michael acceptor Michael acceptor/Alkyl halide Michael acceptor Michael acceptor, Acid halide Michael acceptor/Alkyl halide Michael acceptor/Alkyl halide Michael acceptor (x2) | ⁸¹ |
| Zafirlukast | 8 | 1 3 4 | Acid halide Acid halide, Aromatic nitro Aromatic nitro, Alkyl halide | ⁸² |

⁷⁴ Wallace, M.D.; McGuire, M.a.; Yu, M.S.; Goldfinger, L.; *et al.*, *ibid*, **2004**, 8, 738-743.

⁷⁵ Kobayashi, T.; Masui, Y.; Goto, Y.; Kitaura, Y.; *et al.*, *ibid*, **2004**, 8, 744-753.

⁷⁶ Gala, D.; Dahanukar, V.H.; Eckert, J.M.; Lucas, B.S.; *et al.*, *ibid*, **2004**, 8, 754-768.

⁷⁷ Frey, D.A.; Kataisto, E.W.; Ekmanis, J.L.; O'Malley, S.; *et al.*, *ibid*, **2004**, 8, 796-801.

⁷⁸ Maruyama, N.; Shimizu, H.; Sugiyama, T.; Watanabe, M.; *et al.*, *ibid*, **2004**, 8, 883-888.

⁷⁹ Haight, A.R.; Bailey, A.E.; Baker, W.S.; Cain, M.H.; *et al.*, *ibid*, **2004**, 8, 897-902.

⁸⁰ Provencal, D.P.; Gesenberg, K.D.; Wang, H.; Escobar, C.; *et al.*, *ibid*, **2004**, 8, 903-908.

⁸¹ Fujimoto, M.; Maeda, T.; Okumura, K.; Uda, M.; *et al.*, *ibid*, **2004**, 8, 915-919.

⁸² Srinivas, K.; Srinivasan, N.; Krishna, M.R.; Reddy, C.R.; *et al.*, *ibid*, **2004**, 8, 952-954.

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|--|--|--------|---|--|
| | | 5 6 | Aromatic nitro Aromatic amine, Acid halide | |
|--|--|--------|---|--|

(a). Crystallization/salt formation is counted as a single stage, (b). Reaction of phosphoric acid with alcohol solvent, (c). Highly convergent synthesis, (d). Reaction of sulfuric acid with alcohol solvent, (e). *In situ* formation of a per-acid (reaction of hydrogen peroxide/acid), (f). Highly toxic brucine is used as a resolving agent, (g). ETS (Ethyl toxic acid) formed from reaction of toxic acid with alcohol solvent, (h). DMCC (Dimethylcarbamoyl chloride), (i) TSC (tosyl chloride), (j). Bi-product formed from ring opening of epoxide, (k). Reaction of HCl with alcohol solvent, (l). NBS (*N*-Bromosuccinimide), (m). DNBS (Dinitrobenzenesulfonic acid), (n). Article primarily describes synthesis of penultimate amine hydrochloride precursor, (o). No details provided of first 7 steps.

**Table S-5: Summary of Reactive Intermediates Utilized in Multi-Stage Syntheses during 2005
(Reported in Organic Process R&D)**

| Drug Substance | No. of Synthetic stages ^a | Stage that Reactive Intermediate Introduced | Nature of Reactive intermediate | Reference |
|-------------------------|--------------------------------------|---|---|---------------|
| ABT-239 | 4 | 1 3 4 | NIS ^b TSC ^c Sulfonate ester, Styrene ^d | ⁸³ |
| RO3203546 | 4 | 1 2 3 4 | Formamide Substituted pyrimidine, Acid halide Substituted pyrimidine Substituted pyrimidine | ⁸⁴ |
| Sildenafil ^e | 4 | 1 1 ^f 2 ^f 4 | Chlorosulfonic acid Aromatic nitro/Michael acceptor Aromatic amine/ Michael acceptor Substituted pyrimidine | ⁸⁵ |
| Vardenafil ^e | 6 | 1 2 1' ^f 2' ^f 3 4 5 | Acid halide Hydrazine Acid halide, Alkyl halide Acid halide Hydrazide Acid halide Chlorosulfonic acid | ⁸⁶ |
| Tadalafil ^e | 3 | 1 2 3 | Aromatic aldehyde Acid halide Alkyl halide | ⁸⁷ |
| CCR5 Antagonist | 8 | 4 5 7 8 | Aromatic aldehyde Aromatic aldehyde Acid halide, DMCC ^g Aromatic amine Boronic acid | ⁸⁸ |
| Micafungin ^h | 6 | 1 2 3 1' ^f | Aromatic aldehyde, Hydroxamine Oxime Haloxime Alkyl halide | ⁸⁹ |
| Trecetilide | 4 | 2 4 | Alkyl halide Michael acceptor | ⁹⁰ |
| Oxcarbazepine | 5 | 1 3 5 | Cyanogen chloride Alkyl halide ⁱ Michael acceptor | ⁹¹ |
| Maxacalcitol | 11 | 1 | Alkyl halide | ⁹² |

⁸³Pu, Y.-M.; Grieme, T.; Gupta, A.; Plata, D.; *et al.*, *ibid*, **2005**, 9, 45-50.

⁸⁴Connolly, T.J.; Matchett, M.; Sarma, K.; *ibid*, **2005**, 9, 80-87.

⁸⁵Dunn, P.J.; *ibid*, **2005**, 9, 88-97.

⁸⁶Dunn, P.J.; *ibid*, **2005**, 9, 88-97.

⁸⁷Dunn, P.J.; *ibid*, **2005**, 9, 88-97.

⁸⁸Ikemoto, T.; Ito, T.; Nishiguchi, A.; Miura, S.; *et al.*, *ibid*, **2005**, 9, 168-173.

⁸⁹Ohigashi, A.; Kanda, A.; Tsuboi, H.; Hashimoto, N.; *ibid*, **2005**, 9, 179-184.

⁹⁰Mackey, S.S.; Wu, H.; Matisen, M.E.; Goble, M.; *et al.*, *ibid*, **2005**, 9, 174-178.

⁹¹Fuenfschilling, P.C.; Zaugg, W.; Beutler, U.; Kauffmann, D.; *et al.*, *ibid*, **2005**, 9, 272-277.

| | | | | |
|---|---|--|--|----------------|
| | | 3 5 6 | NBS ^j Peroxide Alkyl halide | |
| Isotretinoin | 2 | 1 2 | Michael acceptor Michael acceptor (x3) | ⁹³ |
| Tolterodine | 6 | 1 2 4 5 | Michael acceptor Alkyl halide TSC ^c Sulfonate ester | ⁹⁴ |
| CP-724714 | 6 | 1 2 4 4' ^f 5 6 | Aromatic amine, Fomamide Acid halide Aromatic amine Aromatic nitro Alkyl halide ⁱ Sulfonate ester ^k | ⁹⁵ |
| CP-481715 | 4 | 1 3 | Alkyl halide Acid Halide | ⁹⁶ |
| Substance P Antagonist | 4 | 1 2 3 4 | Alkyl halide Acid halide Diazonium Michael acceptor | ⁹⁷ |
| JB95008 | 5 | 1 3 | Aromatic amine Michael acceptor | ⁹⁸ |
| 5HT2c agonist ^l | 7 | 1 3 4 5 6 | Aromatic amine Alkyl halide Alkyl halide Alkyl halide Alkyl halide | ⁹⁹ |
| AZD4407 | 2 | 1 | DMDS ^m , DMS ⁿ | ¹⁰⁰ |
| Sulphostin | 6 | 1 4 | Acid halide Acid halide, Alkyl halide | ¹⁰¹ |
| Methyl -1(2,3,5-tri-O-acetyl-β-L-ribofuranosyl)1,2,4-triazole-3-carboxylate | 1 | 1 | Aromatic nitro | ¹⁰² |
| MMP090 | 7 | 2 3 6 | DES ^o , Acid halide ⁱ Alkyl halide Acid halide | ¹⁰³ |

⁹²Shimizu, H.; Shimizu, K.; Kubodera, N.; Mikami, T.; *et al.*, *ibid*, **2005**, 9, 278-287.

⁹³Salman, M.; Babu, S.J.; Kaul, V.K.; Ray, P.C.; *et al.*, *ibid*, **2005**, 9, 302-305.

⁹⁴Srinivas, K.; Srinivasan, N.; Reddy, K.S.; Ramakrishna, M.; *et al.*, *ibid*, **2005**, 9, 314-318.

⁹⁵Brown-Ripin, D.H.; Bourassa, D.E.; Brandt, T.; Castaldi, M.J.; *et al.*, *ibid*, **2005**, 9, 440-450.

⁹⁶Li, B.; Andresen, B.; Brown, M.F.; Buzon, R.A.; *et al.*, *ibid*, **2005**, 9, 466-471.

⁹⁷Journet, M.; Cai, D.; Hughes, D.L.; Kowal, J.J.; *et al.*, *ibid*, **2005**, 9, 490-498.

⁹⁸Ormerod, D.; Willemse, B.; Mermans, R.; Langens, R.; *et al.*, *ibid*, **2005**, 9, 499-507.

⁹⁹Peters, R.; Waldmeier, P.; Joncour, A.; *ibid*, **2005**, 9, 508-512.

¹⁰⁰Alcaraz, M-L.; Atkinson, S.; Cornwall, P.; Foster, A.C.; *et al.*, *ibid*, **2005**, 9, 555-569.

¹⁰¹Abe, M.; Nagai, M.; Yamamoto, K.; Yamazaki, H.; *et al.*, *ibid*, **2005**, 9, 570-576.

¹⁰²Zhang, P.; Dong, Z.E.; Cleary, T.P.; *ibid*, **2005**, 9, 583-592.

¹⁰³Slade, J.S.; Vivelo, J.A.; Parker, D.J.; Bajwe, J.; *et al.*, *ibid*, **2005**, 9, 608-620.

| | | | | |
|------------------------------------|---|---------------------------------|---|----------------|
| | | 7 | Acid halide, Hydroxylamine, Alkyl halide ⁱ , Hydroxamic acid | |
| LY503430 | 8 | 1 2 3 4 5 7 8 | Alkyl halide NBS ^j Alkyl halide, Michael acceptor Michael acceptor, Hydrazine Acid halide Boronic acid Acid halide | ¹⁰⁴ |
| Sitagliptan | 7 | 1 2 3 4 7 | Hydrazine Hydrazide Hydrazide Acid halide ⁱ , Purine analogue Alkyl phosphate ^p | ¹⁰⁵ |
| Tazarotene | 4 | 1 2 | Acid halide Acid halide | ¹⁰⁶ |
| UK 350926 | 5 | 1 2 4 | Alkyl halide Alkyl halide Acid halide | ¹⁰⁷ |
| 2 (S)-Amino-6-borono-hexanoic acid | 3 | 1 3 | Alkyl halide Alky halide ⁱ , Boronic acid | ¹⁰⁸ |
| ONO-2506 | 6 | 1 2 3 4 5 | Epoxide Acid halide/aromatic nitro Aromatic nitro TSC ^c Sulfonate ester | ¹⁰⁹ |
| Thalidomide | 2 | 1 2 | Michael acceptor, Acid halide Michael acceptor (x2) | ¹¹⁰ |

(a). Crystallization/salt formation is counted as a single stage, (b). NIS (*N*-iodosuccinimide), (c). TSC (tosyl chloride), (d). final stage impurity, (e). Same publication (but split out into three separate entries for clarity), (f). Parallel side chain reaction, (g). DMCC (Dimethyl carbamoyl chloride - reaction between thionyl chloride and DMF), (h). Most of publication centred on side chain which is coupled at last stage, (i). Reaction of HCl with alcohol solvent, (j). NBS (*N*-bromosuccinimide), (k). Reaction of methanesulfonic acid with alcohol solvent, (l). Principally focussed on synthesis of penultimate stage of API, (m). DMDS (dimethyl disulfide), (n). DMS (dimethyl sulphide) (o). DES (diethyl sulphate), (p). Reaction of phosphoric acid with alcohol solvent.

¹⁰⁴ Magnus, M.A.; Aikins, J.A.; Cronin, J.S.; Diseroad, W.D.; *et al.*, *ibid*, **2005**, 9, 621-628.

¹⁰⁵ Hansen, K.B.; Balsells, J.; Dreher, S.; Hsiao, Y.; *et al.*, *ibid*, **2005**, 9, 634-639.

¹⁰⁶ Frigoli, S.; Fuganti, C.; Malpezzi, L.; Serra, S.; *ibid*, **2005**, 9, 646-650.

¹⁰⁷ Ashcroft, C.P.; Challenger, S.; Clifford, D.; Derrick, A.M.; *et al.*, *ibid*, **2005**, 9, 663-669.

¹⁰⁸ Vadon-Legoff, S.; Dijols, S.; Mansuy, D.; Boucher, J-L.; *et al.*, *ibid*, **2005**, 9, 667-679.

¹⁰⁹ Hasegawa, T.; Kawanaka, Y.; Kasamatsu, E.; Ohta, C.; *et al.*, *ibid*, **2005**, 9, 774-781.

¹¹⁰ Varala, R.; Adapa, S.R.; *ibid*, **2005**, 9, 853-856.

**Table S-6: Summary of Reactive Intermediates Utilized in Multi-Stage Syntheses during 2006
(Reported in Organic Process R&D)**

| Drug Substance | No. of Synthetic stages ^a | Stage that Reactive Intermediate Introduced | Nature of Reactive intermediate | Reference |
|--|--------------------------------------|---|--|----------------|
| LSN344309 | 6 | 1 2 | DMS ^b , Alkyl halide Michael acceptor | ¹¹¹ |
| PDE-4 Inhibitor | 6 | 1 2 3 4 5 5' ^e | Aromatic amine, Aromatic nitro, Alkyl mesylate ^c NBS ^d Alkyl halide Boronic acid/Aromatic aldehyde Aromatic aldehyde Hydroxylamine, Oxime | ¹¹² |
| B-Raf Kinase Inhibitor | 4 | 1 4 | Aromatic amine, Alkyl halide ^f Boronic acid | ¹¹³ |
| LBM415 | 7 | 2 3 6' ^e 7 | Michael acceptor Michael acceptor Aromatic amine, Acid chloride Epoxide, Aromatic N-oxide | ¹¹⁴ |
| 5,6-Diethyl-2,3-dihydro-1H-inden-2-amine | 6 | 2 4 | Acid halide Acid halide | ¹¹⁵ |
| Pergolide | 6 | 1 3 4 6 | Cyanogen bromide, Alkyl halide Alkyl aldehyde Alkyl halide Alkyl mesylate ^c | ¹¹⁶ |
| CP-885316 | 4 | 1 2 3 4 | Aromatic amine, Acid chloride Aromatic amine Aromatic amine, Alkyl halide, Alkyl halide ^f Alkyl halide | ¹¹⁷ |
| CCR3 Antagonist | 9 | 6 7 9' ^e | Acid halide Alkyl aldehyde Aromatic amine | ¹¹⁸ |
| PNU288034 | 4 | 2 4 | Aromatic nitro, Acid halide Alkyl halide | ¹¹⁹ |
| Adapalene | 5 | 2 | DMS ^b | ¹²⁰ |
| AG-28262 | 6 | 1 | Alkyl halide | ¹²¹ |

¹¹¹Rasmy, O.M.; Vaid, R.K.; Semo, M.J.; Chelius, E.C.; et al., *ibid*, **2006**, 10, 28-32.

¹¹²Conlon, D.A.; Drahus-Paone, A.; Ho, G-J.; Pipik, B.; et al., *ibid*, **2006**, 10, 36-45.

¹¹³Denni-Dischert, D.; Marterer, W.; Bänzinger, M.; Yusuff, N.; et al., *ibid*, **2006**, 10, 70-77.

¹¹⁴Slade, J.; Parker, D.; Girgis, M.; Mueller, M.; et al., *ibid*, **2006**, 10, 78-93.

¹¹⁵Prashad, M.; Hu, B.; Har, D.; Repič, O.; et al., *ibid*, **2006**, 10, 135-141.

¹¹⁶Cabri, W.; Roletto, J.; Olmo, S.; Fonte, P.; et al., *ibid*, **2006**, 10, 198-202.

¹¹⁷Caron, S.; Do, N.M.; McDermott, R.M.; Bahmanyar, S.; *ibid*, **2006**, 10, 257-261.

¹¹⁸Yue, T-Y.; McLeod, D.D.; Albertson, K.B.; Beck, S.R.; et al., *ibid*, **2006**, 10, 262-271.

¹¹⁹Lu, C.V.; Chen, J.J.; Perrault, W.R.; Conway, W.G.; et al., *ibid*, **2006**, 10, 272-277.

¹²⁰Liu, Z.; Xiang, J.; *ibid*, **2006**, 10, 285-288.

| | | | | |
|------------------------------------|----|---------------------------------------|---|----------------|
| | | 4 5 | Acid halide Michael acceptor | |
| (R)-Sibutramine | 5 | 2 4 | Alkyl aldehyde Alkyl halide ^f | ¹²² |
| PNA-565272A | 5 | 1 2 3 4 5 | Aromatic nitro Aromatic nitro Aromatic nitro Aromatic amine, Diazonium Hydrazide, Alkyl halide | ¹²³ |
| RC-1291 | 4 | 1 2 3 4 | Hydrazide Hydrazide Hydrazide Hydrazide, Michael Acceptor ^g | ¹²⁴ |
| α 1-adrenoceptor antagonist | 5 | 1 2 3 $5'$ ^e 5 | Aromatic nitro Aromatic nitro Aromatic amine Acid halide Substituted pyrimidine | ¹²⁵ |
| GABA α 2/3 agonist | 6 | 1 2 3 4 $5'$ ^e | Aromatic nitro Aromatic nitro Aromatic nitro Aromatic amine, Diazonium Michael acceptor, Aromatic amine, Alkyl aldehyde | ¹²⁶ |
| Torceptrapib | 7 | 1 3 6 7 | Aromatic amine, Alkyl aldehyde Acid halide Aromatic aldehyde Acid Halide | ¹²⁷ |
| Torceptrapib | 10 | 1 6 7 9 10 | Alkyl halide Acid halide Acid Halide Acid Halide Alkyl halide | ¹²⁸ |
| PHA-529311 | 7 | 1 2 3 4 5 6 7 | Alkyl halide/aromatic nitro Aromatic nitro Aromatic amine Aromatic amine Michael acceptor Michael acceptor Michael acceptor | ¹²⁹ |
| ABT-963 | 4 | 1 | Aromatic amine, Diazonium | ¹³⁰ |

¹²¹ Scott, R.W.; Neville, S.N.; Urbino, A.; Camp, D.; et al., *ibid*, **2006**, *10*, 296-303.

¹²² Han, Z.; Krishnamurthy, D.; Senanayake, C.H.; *ibid*, **2006**, *10*, 327-333.

¹²³ Fleck, T.J.; Chen, J.J.; Lu, C.V.; Hanson, K.J.; *ibid*, **2006**, *10*, 334-338.

¹²⁴ Paul, B.J.; Littler, B.J.; Jos, F.; Vogt, P.F.; *ibid*, **2006**, *10*, 339-345.

¹²⁵ Connolly, T.J.; Matchett, M.; McGarry, P.; Sukhtankar, S.; et al., *ibid*, **2006**, *10*, 391-397.

¹²⁶ Cameron, M.; Foster, B.S.; Lynch, J.E.; Shi, Y-J.; et al., *ibid*, **2006**, *10*, 398-402.

¹²⁷ Damon, D.B.; Dugger, R.W.; Magnus-Aryitey, G.; Ruggeri, R.B.; et al., *ibid*, **2006**, *10*, 464-471.

¹²⁸ Damon, D.B.; Dugger, R.W.; Hubbs, S.E.; Scott, J.M.; et al., *ibid*, **2006**, *10*, 472-480.

¹²⁹ Dorow, R.L.; Herrinton, P.M.; Hohler, R.A.; Maloney, M.T.; et al., *ibid*, **2006**, *10*, 493-499.

¹³⁰ Keredsky, F.A.J.; Leanna, M.R.; Zhang, J.; Ki, W.; et al., *ibid*, **2006**, *10*, 512-517.

| | | | | |
|--------------------------------------|---|---------------------------------|--|----------------|
| | | 2 3 4 | Michael acceptor Michael acceptor, Boronic acid Michael acceptor | |
| 479754 | 4 | 2 ^e 3 4 | Aromatic amine Aromatic amine, Aromatic aldehyde Aromatic amine | ¹³¹ |
| ABT-492 | 7 | 1 2 3 4 5 6 7 | Aromatic amine Michael acceptor Michael acceptor/Aromatic amine Aromatic amine Aromatic amine Aromatic amine Aromatic amine | ¹³² |
| LY290154 | 5 | 1 3 4' ^e | Aromatic aldehyde Acid halide Alkyl halide | ¹³³ |
| Hepatitis Polymerase Inhibitor | 6 | 1 2 3 4 5 6 | Michael acceptor, Michael acceptor Michael acceptor Michael acceptor Michael acceptor, Aromatic aldehyde/Purine analogue Michael acceptor/Purine analogue Michael acceptor/Purine analogue | ¹³⁴ |
| NPY-5 Receptor Antagonist | 4 | 1 2 3 | Aromatic amine Aromatic amine, Boronic acid Aromatic amine, Acid chloride | ¹³⁵ |
| LB30057 | 6 | 1 4 5 | Alkyl halide, Acid halide Acid halide Acid halide, Hydrazine Hydrazide (x2), Michael receptor ^g | ¹³⁶ |
| CTDP 31446 | 5 | 5 | Alkyl halide ^f | ¹³⁷ |
| RWJ-333966 | 5 | 2 3 4 5 | Alkyl halide Michael acceptor Michael acceptor, Isothiocyanate Michael acceptor | ¹³⁸ |

(a). Crystallization/salt formation is counted as a single stage, (b). DMS (dimethyl sulphate), (c). Reaction of methanesulfonic acid with alcohol solvent, (d). NBS (*N*-bromosuccinimide), (e). Parallel side chain reaction, (f). Reaction of HCl with alcohol solvent, (g). Counter-ion (fumaric acid).

¹³¹ Magnus, M.A.; Diserod, W.D.; Nevill, C.R.; Wepseic, J.P.; *ibid*, **2006**, *10*, 556-560.

¹³² Height, A.R.; Ariman, S.Z.; Barnes, D.M.; Benz, N.J.; *et al.*, *ibid*, **2006**, *10*, 751-756.

¹³³ Merschaert, A.; Boquel, P.; Van Hoek, J.-P.; Gorrisen, H.; Borghese, A.; *et al.*, *ibid*, **2006**, *10*, 776-783.

¹³⁴ Camp, D.; Matthews, C.F.; Neville, S.T.; Rouns, R.; *et al.*, *ibid*, **2006**, *10*, 814-821.

¹³⁵ Itoh, T.; Kato, S.; Nonoyama, N.; Wada, T.; *et al.*, *ibid*, **2006**, *10*, 822-828.

¹³⁶ Kim, B.C.; Hwang, S.Y.; Lee, T.H.; Chang, J.H.; *et al.*, *ibid*, **2006**, *10*, 881-886.

¹³⁷ Mobele, B.I.; Kinahan, T.; Ulysse, L.G.; Gagnier, S.V.; *ibid*, **2006**, *10*, 881-886.

¹³⁸ Guillaume, M.; *ibid*, **2006**, *10*, 1127-1230.

**Table S-7: Summary of Reactive Intermediates Utilized in Multi-Stage Syntheses during 2007
(Reported in Organic Process R&D)**

| Drug Substance | No. of Synthetic stages ^a | Stage that Reactive Intermediate Introduced | Nature of Reactive intermediate | Reference |
|------------------------------------|--------------------------------------|---|---|----------------|
| Fluvastatin | 3 | 1 | Michael acceptor/Alkyl aldehyde | ¹³⁹ |
| | | 2 | Michael acceptor Peroxide, Michael acceptor ^b | |
| AG035029 | 9 | 2 | Alkyl halide, alkyl tosylate ^c | ¹⁴⁰ |
| | | 4 | Alkyl halide | |
| | | 5 | Aromatic nitro | |
| | | 6 | Aromatic nitro | |
| | | 7 | Aromatic amine | |
| | | 8 | Michael acceptor | |
| Telmisartan | 7 | 1 | Aromatic amine, Acid halide | ¹⁴¹ |
| | | 3 | Aromatic nitro | |
| | | 4 | Aromatic amine | |
| | | 6 | Aromatic amine | |
| | | 7 | Alkyl halide | |
| Lobeglitazone sulfate | 5 | 3 | Aromatic aldehyde | ¹⁴² |
| | | 4 | Aromatic aldehyde | |
| | | 5 | Michael acceptor, Alkyl sulfate ^d | |
| ZK 191784 | 4 ^e | 2 | Michael acceptor | ¹⁴³ |
| | | 4 | Michael acceptor | |
| C ₁₇₋₂₀ Lyase Inhibitor | 5 | 1 | Aromatic aldehyde, Alkyl halide | ¹⁴⁴ |
| | | 2 | Aromatic aldehyde | |
| MLN1251 | 5 | 1 | Michael acceptor | ¹⁴⁵ |
| | | 3 | Michael acceptor, Benzoquinone | |
| | | 4 | Acid halide | |
| STA-5312 | 5 | 1 | Alkyl halide | ¹⁴⁶ |
| | | 2 | Alkyl tosylate ^c | |
| | | 3 | Alkyl halide | |
| | | 4 | Acid halide (x2) | |
| Memantine HCL | 4 | 2 | Alkyl halide | ¹⁴⁷ |
| Artemether | 2 | 2 | Alkyl halide ^f | ¹⁴⁸ |
| Lumefantrine | 7 | 2 | Acid halide/Alkyl halide | ¹⁴⁹ |
| | | 3 | Alkyl halide | |

¹³⁹Fuenfschilling, P.C.; Hoehn, P.; Mutz, J-P.; *ibid*, **2007**, 11, 13-18.

¹⁴⁰Saenz, J.; Mitchell, M.; Bahmanyar, S.; Stankovic, N.; et al., *ibid*, **2007**, 11, 30-38.

¹⁴¹Reddy, K.S.; Srinivasan, N.; Reddy, C.R.; Kolla, N.; et al., *ibid*, **2007**, 11, 81-85.

¹⁴²Lee, H.W.; Ahn, J.B.; Kang, S.K.; Ahn, S.K.; et al., *ibid*, **2007**, 11, 190-199.

¹⁴³Westermann, J.; Schneider, M.; Platzek, J.; Petrov, O.; *ibid*, **2007**, 11, 200-205.

¹⁴⁴Kawakami, J-I.; Kimura, K.; Yamaoka, M.; *ibid*, **2007**, 11, 206-209.

¹⁴⁵Rönn, M.; McCubbin, Q.; Winter, S.; Veige, M.K.; et al., *ibid*, **2007**, 11, 241-245.

¹⁴⁶Li, H.; Xia, Z.; Chen, S.; Koya, K.; et al., *ibid*, **2007**, 11, 246-250.

¹⁴⁷Reddy, J.M.; Prasad, G.; Raju, V.; Ravikumar, M.; et al., *ibid*, **2007**, 11, 268-269.

¹⁴⁸Boehm, M.; Fuenfschilling, P.C.; Krieger, M.; Kuesters, E.; et al., *ibid*, **2007**, 11, 336-340.

¹⁴⁹Beutler, U.; Fuenfschilling, P.C.; Steinkemper, A.; et al., *ibid*, **2007**, 11, 341-345.

| | | | | |
|-----------------------|----|--|---|----------------|
| | | 4 5 6 | Alkyl halide Epoxide Aromatic aldehyde | |
| Reboxetine Mesylate | 9 | 1 2 3 4 6 7 8 | Epoxide Epoxide Acid halide/Aromatic nitro Alkyl halide Epoxide Acid halide/Alkyl halide Alkyl halide | ¹⁵⁰ |
| Oxandrolone | 4 | 2 3 4 | Alkyl halide Michael acceptor Alkyl aldehyde | ¹⁵¹ |
| Isothiazoloquinolone | 13 | 1 2 4 5 6 9 12 13 | Acid halide Acid halide Isothiocyanate Michael acceptor, Alkyl halide Michael acceptor Hydroxylamine Aromatic amine Boronic acid | ¹⁵² |
| SERM ^g | 10 | 2 3 4 5 6 7 | Michael acceptor Michael acceptor Michael acceptor, NBS ^h Michael acceptor, Alkyl halide Michael acceptor, Alkyl halide Michael acceptor | ¹⁵³ |
| LY518674 | 4 | 1 2 3 | Hydrazide, Isocyanate Hydrazide Alkyl sulfate ^d , Alkyl halide | ¹⁵⁴ |
| Ro 24-5904 | 5 | 1 2 3 4 5 | Aromatic nitro/Aromatic aldehyde Aromatic nitro/Michael acceptor, Acid halide Aromatic nitro/Michael acceptor/Acid halide Aromatic nitro/Michael acceptor Aromatic nitro/Michael acceptor, Alkyl halide, Aromatic nitro | ¹⁵⁵ |
| Clopidogrel Bisulfate | 5 | 2 5 | Alkyl halide DMS ⁱ | ¹⁵⁶ |
| ABT-472 | 8 | 1 2 3 | Aromatic nitro Aromatic nitro/Michael acceptor Aromatic nitro | ¹⁵⁷ |

¹⁵⁰ Henegar, K.E.; Ball, C.T.; Horvarth, C.M.; Maisto, K.D.; et al., *ibid*, **2007**, 11, 346-353.

¹⁵¹ Cabaj, J.E.; Kairys, K.; Benson, T.R.; *ibid*, **2007**, 11, 378-388.

¹⁵² Hashimoto, A.; Pais, G.C.G.; Wang, Q.; Lucien, E.; et al., *ibid*, **2007**, 11, 389-398.

¹⁵³ Li, X.; Reuman, M.; Russell, R.K.; Adams, R.; et al., *ibid*, **2007**, 11, 414-421.

¹⁵⁴ Braden, T.M.; Coffey, D.S.; Doecke, C.W.; LeTourneau, M.E.; et al., *ibid*, **2007**, 11, 431-440.

¹⁵⁵ Kuzemko, M.A.; Van Arnum, S.D.; Niemczyk, H.J.; *ibid*, **2007**, 11, 470-476.

¹⁵⁶ Wang, L.; Shen, J.; Tang, Y.; Chen, Y.; et al., *ibid*, **2007**, 11, 487-489.

¹⁵⁷ Barkalow, J.H.; Breting, J.; Gaede, B.J.; Haight, A.R.; et al., *ibid*, **2007**, 11, 693-698.

| | | | | |
|-------------------------|----|--|---|----------------|
| | | 4 5 6 6' ^j 7 | Aromatic nitro/Aromatic amine, Acid halide Aromatic nitro/Aromatic amine Aromatic amine (x2) Alkyl aldehyde Aromatic amine | |
| Laquinimod | 2 | 1 2 | Aromatic amine, Acid Halide Alkyl halide, Michael acceptor | ¹⁵⁸ |
| ABT-102 | 7 | 1 2 3 4 | Aromatic nitro/Aromatic amine Aromatic nitro/Aromatic triazene Aromatic nitro/Acid halide Aromatic amine | ¹⁵⁹ |
| R,S-N-methyl sertraline | 6 | 1 2 3 4 5 | Michael acceptor ^k Michael acceptor ^k Alkyl halide ^f , Aldehyde ^l Aldehyde ^l | ¹⁶⁰ |
| SERM ^g | 9 | 2 3 4 5 6 | Michael acceptor, Alkyl halide Michael acceptor Michael acceptor Michael acceptor, Alkyl halide Michael acceptor | ¹⁶¹ |
| DG-041 | 6 | 1 3 3' ^k 4 5 6 | Aromatic amine, Vinyl halide Methyl acrylate Aromatic nitro, Vinyl halide Michael acceptor Michael acceptor Michael acceptor, Alkyl halide | ¹⁶² |
| CP-865,569 | 6 | 1 2 3 4 5 | Alkyl halide Acid halide Aromatic aldehyde Alkyl halide Acid halide | ¹⁶³ |
| Meropenem | 2 | 1 | Aryl phosphonate | ¹⁶⁴ |
| Gefitinib | 3 | 1 2 3 | Aromatic nitro Aromatic amine Aromatic amine | ¹⁶⁵ |
| AEW541 | 12 | 1 3 4 7 8 | Alkyl halide Alkyl halide, Diazonium Diazonium, Alky halide ^f Aromatic amine Aromatic amine | ¹⁶⁶ |

¹⁵⁸ Wennerberg, J.; Björk, A.; Fristedt, T.; Granquist, B.; *et al.*, *ibid*, **2007**, *11*, 674-680.

¹⁵⁹ Lukin, K.; Hsu, M.C.; Chambournier, G.; Kotecki, B.; *et al.*, *ibid*, **2007**, *11*, 578-584.

¹⁶⁰ Han, Z.; Koenig, S.G.; Zhao, H.; Su, X.; Singh, S.P.; *et al.*, *ibid*, **2007**, *11*, 726-730.

¹⁶¹ Li, X.; Reuman, M.; Russell, R.K.; Youells, S.; *et al.*, *ibid*, **2007**, *11*, 731-738.

¹⁶² Zegar, S.; Tokar, C.; Enache, L.A.; Rajagopol, V.; *et al.*, *ibid*, **2007**, *11*, 747-753.

¹⁶³ Belecki, K.; Berliner, M.; Bibart, R.T.; Meltz, C.; *et al.*, *ibid*, **2007**, *11*, 754-761.

¹⁶⁴ Tewari, N.; Nizar, H.; Rai, B.P.; Singh, S.K.; *et al.*, *ibid*, **2007**, *11*, 773-775.

¹⁶⁵ Chandregowda, V.; Rao, G.V.; Reddy, G.C.; *ibid*, **2007**, *11*, 813-816.

¹⁶⁶ Slade, J.; Bajwa, J.; Liu, H.; Parker, D.; *et al.*, *ibid*, **2007**, *11*, 825-835.

| | | | | |
|--|----|---|--|----------------|
| | | 1' ^k 2' ^k 4' ^k 6' ^k 9 10 11 12 | Epoxide/Alkyl halide, Alkyl halide Alkyl halide (x2) Alky halide ^f Alkyl halide Aromatic amine Aromatic amine Aromatic amine, Alkyl halide Aromatic amine, Azetidine | |
| Dutasteride | 7 | 1 2 4 6 7 | Michael acceptor Michael acceptor Alkyl sulfate ^h Michael acceptor Michael acceptor (x2), Aromatic amine, Acid halide | ¹⁶⁷ |
| 5-(3-Fluorophenyl)-2,4-dihydro-2,4-dimethyl-3H-1,2,4-triazole-3-thione | 2 | 1 2 | Hydrazide, Acid halide Hydrazide | ¹⁶⁸ |
| Valsartan | 5 | 1 2 3 4 | Azide Alkyl halide Acid halide Azide | ¹⁶⁹ |
| Rimonabant | 6 | 2 3 5 6 | Hydrazide Hydrazide Acid halide Acid halide | ¹⁷⁰ |
| 5HT _{2c} | 13 | 1 2 3 4 6 7 12 | Acid halide Alkyl halide (x2) Alkyl halide Alkyl halide ^f <i>N</i> -Nitroso Hydrazide Boronic acid | ¹⁷¹ |
| Naphthalenoid H ₃ antagonist | 8 | 2 3 4 6 7 8 | Acid halide Alkyl halide Alkyl sulphate ^d Michael acceptor Michael acceptor, Alkyl halide Michael acceptor (x2), Alkyl halide ^f | ¹⁷² |
| PPAR _{αδ} Agonist | 5 | 1 1' 2' | Acid halide Alkyl halide Epoxide | ¹⁷³ |

¹⁶⁷Satyanarayana, K.; Srinivas, K.; Himabindu, V.; Reddy, G.M.; *ibid*, **2007**, 11, 842-845 .

¹⁶⁸Louks, D.H.; Stoltz-Dunn, S.K.; *ibid*, **2007**, 11, 887-884 .

¹⁶⁹Beutler, U.; Boehm, M.; Fuenfschilling, P.C.; Heinz, T.; *et al.*, *ibid*, **2007**, 11, 892-890.

¹⁷⁰Kotagiri, V.K.; Suthrapu, S.; Reddy, J.M.; Rao, C.P.; *et al.*, *ibid*, **2007**, 11, 910-912.

¹⁷¹Hobson, L.A.; Nugent, W.A.; Anderson, S.R.; Deshmukh, S.S.; *et al.*, *ibid*, **2007**, 11, 985-995.

¹⁷²Pu,Y-M.; Ku, Y-Y.; Grieme, T.; Black, L.A.; *et al.*, *ibid*, **2007**, 11, 1004-1009.

¹⁷³Reuman, M.; Hu, Z.; Kuo, G-H.; Li, X.; *et al.*, *ibid*, **2007**, 11, 1010-1014.

| | | | | |
|---|----|------------------|---|----------------|
| | | 4 | Alkyl halide | |
| CJ-17,493 | 7 | 2 3 5 6 | Alkyl halide Acid halide Alkyl halide Alkyl halide | ¹⁷⁴ |
| GSK183390 | 7 | 2 3 4 7 | Hydrazine Hydroxylamine Acid halide Acid halide | ¹⁷⁵ |
| Dual SSRI/Histamine H ₃ antagonist | 4 | 1 2 3 4 | Alkyl halide Alkyl halide Alkyl halide ^f , Alkyl mesylate ^m Alkyl halide | ¹⁷⁶ |
| R116301 | 10 | 4 9 | Acid halide Acid halide/Aromatic amine | ¹⁷⁷ |
| Obatoclax | 3 | 1 2 3 | Michael acceptor, Acid halide Boronic acid Alkyl halide ^f | ¹⁷⁸ |

(a). Crystallization/salt formation is counted as a single stage, (b). Impurity in stage 2, (c). Reaction of tosic acid with alcohol solvent, (d). Reaction of sulfuric acid with alcohol solvent, (e). Registered starting material is vitamin D2 (3) via involves 7-synthetic stages to aldehyde (4); However, no synthetic details are provided so assessment uses aldehyde (4) as starting material, (f). Reaction of HX with alcohol solvent, (g). SERM (Selective Estrogen Receptor Modulator), (h). NBS (*N*-bromosuccinimide), (i). DMS (dimethyl sulphate), (j). Reagent used in formation of side chain, (k).Sulfinyl imine, (l). *N*-formyl amine, (m). Reaction of methanesulfonic acid with alcohol solvent.

¹⁷⁴Caron, S.; Do, N.M.; Sieser, J.E.; Arpin, P.; et al. *ibid*, **2007**, *11*, 1015-1024.

¹⁷⁵Oh, L.M.; Wang, H.; Shilcrat, S.M.; Hermann, R.E.; et al., *ibid*, **2007**, *11*, 1032-1042.

¹⁷⁶Deng, X.; Liang, J.T.; McAllister, H.; Schubert, C.; et al., *ibid*, **2007**, *11*, 1043-1050.

¹⁷⁷Guillaume, M.; Cuypers, J.; Dingenen, J.; *ibid*, **2007**, *11*, 1079-1086.

¹⁷⁸Dairi, K.; Yao, Y.; Faley, M.; Tripathy, S.; et al., *ibid*, **2007**, *11*, 1051-1054.

**Table S-8: Summary of Reactive Intermediates Utilized in Multi-Stage Syntheses during 2008
(Reported in Organic Process R&D)**

| Drug Substance | No. of Synthetic stages ^a | Stage that Reactive Intermediate Introduced | Nature of Reactive intermediate | Reference |
|--|--------------------------------------|---|---|----------------|
| Atazanavir | 4 | 1 2 3 | Hydrazine Hydrazide, Epoxide Hydrazide | ¹⁷⁹ |
| WAY-253752 | 5 | 1 3 4 | Hydrazine Benzene Alkyl aldehyde | ¹⁸⁰ |
| <i>N</i> -[5-(3-imidazol-1-yl-4-methanesulfonyl-phenyl)-4-methyl-thiazol-2-yl) acetamide | 5 | 1 2 3 5 | Aromatic aldehyde Aromatic aldehyde, Alkyl nitro Aromatic nitro Alkyl halide, Thiourea | ¹⁸¹ |
| SSRI ^b | 4 | 1 2 3 4 | Alkyl halide, Acid halide Aromatic aldehyde Michael acceptor, Acid halide Alkyl aldehyde | ¹⁸² |
| SSRI ^b | 7 | 1 2 3 4 6 7 | Vinyl halide, TsCl ^c Sulfonate ester Michael acceptor/Alkyl aldehyde Michael acceptor/Alkyl aldehyde, alkyl halide ^d Alkyl aldehyde, Acid halide Acid halide | ¹⁸³ |
| LCD320 | 8 | 1 2 3 4 6 7 8 | Alky halide Alkyl aldehyde Michael acceptor, Acid halide Michael acceptor, Hydroxylamine MSC MSCe <i>N</i> -formyl | ¹⁸⁴ |
| Asenapine maleate | 5 | 1 4 5 | Acid halide Michael acceptor, Alky halide Michael acceptor ^e | ¹⁸⁵ |
| AZD3409 | 7 | 1 3 | MSC Aromatic amine | ¹⁸⁶ |
| LY2497282 | 7 | 1 | Aromatic aldehyde | ¹⁸⁷ |

¹⁷⁹Fan, X.; Song, Y-L, Long, Y-Q.; *ibid*, **2008**, 12, 69-75

¹⁸⁰Nikitenko, A.; Evard, D.; Sabb, A.L.; Vogel, R.L.; *et al.*, *ibid*, **2008**, 12, 76-80

¹⁸¹Hirt, H.; Haenggi, R.; Reyes, J.; Seeger-Weibel, M.; *et al.*, *ibid*, **2008**, 12, 111-115

¹⁸²Anthes, R.; Bello, O.; Benoit, S.; Chen, C-K.; *et al.*, *ibid*, **2008**, 12, 168-177

¹⁸³Anthes, R.; Benoit, S.; Chen, C-K.; Corbett, E.A.; *et al.*, *ibid*, **2008**, 12, 178-182

¹⁸⁴Liu, Y.; Prashad, M.; Ciszewski, L.; Vargas, K.; *et al.*, *ibid*, **2008**, 12, 183-191

¹⁸⁵Van der Linden, M.; Roeters, T.; Harting, R.; Stokkingreef, E.; *et al.*, *ibid*, **2008**, 12, 196-201

¹⁸⁶Abbas, S.; Ferris, L.; Norton, A.K.; Powell, L.; *et al.*, *ibid*, **2008**, 12, 202-212

| | | | | |
|----------------------|----|-------------------------------------|---|----------------|
| | | 2 | Michael acceptor | |
| AMP-DNM | 12 | 7 8 9 10 12 | Alkyl halide ^d Alkyl aldehyde MSC Alkyl aldehyde Alkyl halide ^d | ¹⁸⁸ |
| Lu AA26778 | 10 | 1 2 7 | Michael acceptor Michael acceptor Dimethyl sulphide, MSC | ¹⁸⁹ |
| Imatinib | 4 | 1 2 2' ^g 3 4 | Aromatic amine/Aromatic nitro, Alkyl nitrate ^f Aromatic nitro, Michael acceptor Michael acceptor Aromatic nitro Aromatic amine, Acid halide | ¹⁹⁰ |
| UK-371,104 | 6 | 1 2 3 4 5 6 | Purine analogue/Aromatic amine Purine analogue/Aromatic amine, Acid halide Purine analogue/Aromatic amine, Acid halide Purine analogue Purine analogue Purine analogue | ¹⁹¹ |
| MN-477 | 6 | 1 3 4 | Alkyl halide MSC Pyrimidine analogue | ¹⁹² |
| LC15,0133 | 6 | 1 2 5 6 | Alkyl halide ^d Alkyl halide, Michael acceptor Acid halide Alkyl halide | ¹⁹³ |
| Merimepodib (VX-497) | 4 | 2 3 3' ^g 4 | Aromatic amine Aromatic amine, Acid halide Aromatic nitro Aromatic amine | ¹⁹⁴ |
| AMD070 | 5 | 2 4 5 | Alkyl aldehyde, Michael receptor Alkyl halide Hydrazine | ¹⁹⁵ |
| Swainsonine | 9 | 2 3 8 | TsCL ^c Sulfonate ester, Diazonium Peroxide | ¹⁹⁶ |
| Oxazolidinone | 5 | 1 | Aromatic nitro | ¹⁹⁷ |

¹⁸⁷Yu, H.; Richey, R.N.; Stout, J.R.; LaPack, M.A.; et al., *ibid*, **2008**, 12, 218-225.

¹⁸⁸Wennekes, T.; Lang, B.; Leeman, M.; van der Marel, G.A.; et al., *ibid*, **2008**, 12, 414-423.

¹⁸⁹Dahl, A.C.; Mealy, M.J.; Nielsen, M.A.; Lyngsø, L.A.; et al., *ibid*, **2008**, 12, 429-441.

¹⁹⁰Liu, Y-F.; Wang, C-L.; Bai, Y-J.; Han, N.; et al., *ibid*, **2008**, 12, 490-495.

¹⁹¹Challenger, S.; Densi, Y.; Fox, D.E.; Hesmondhalgh, L.C.; et al., *ibid*, **2008**, 12, 575-583.

¹⁹²Ishikawa, M.; Tsushima, M.; Kubota, D.; Yanagisawa, Y.; et al., *ibid*, **2008**, 12, 596-602.

¹⁹³Kim, B.C.; Kim, K-Y.; Lee, H.B.; Shin, H.; *ibid*, **2008**, 12, 626-631.

¹⁹⁴Looker, A.R.; Littler, B.J.; Blythe, T.A.; Snoonian, J.R.; *ibid*, **2008**, 12, 666-673

¹⁹⁵Crawford, J.B.; Chen, G.; Gauthier, D.; Wilson, T.; Carpenter, B.; et al., *ibid*, **2008**, 12, 823-830.

¹⁹⁶Sharma, P.K.; Shah, R.N.; Carver, J.P.; *ibid*, **2008**, 12, 831-836

| | | | | |
|-----------------------------|----|---------------------------------------|--|----------------|
| Antibacterial | | 2 3 4 | Aromatic nitro, Acid halide/alkyl halide Aromatic nitro/alkyl halide Aromatic amine, Epoxide | |
| Gemcitabine | 8 | 1 4 5 6 7 8 | Acid halide MSC Sulfonate ester, Pyrimidine analogue Pyrimidine analogue Pyrimidine analogue/Aromatic amine, alkyl halide ^d Pyrimidine analogue/Aromatic amine (x2) | ¹⁹⁸ |
| NBI-75043 | 7 | 1 2 | Alkyl halide Michael acceptor | ¹⁹⁹ |
| Maraviroc (UK-427,857) | 8 | 1 2 3 4 6 8 | Alkyl aldehyde, Hydroxylamine Oxime Acid halide Acid halide, Hydrazide Alkyl aldehyde Acid halide | ²⁰⁰ |
| Maraviroc (UK-427,857) | 4 | 1 4 4' | Acid halide Alkyl aldehyde MTA ^h | ²⁰¹ |
| BYK 405879 | 15 | 1 2 3 4 5 6 9 12 | Aromatic nitro/Aromatic amine, Acid halide Aromatic nitro/Aromatic amine, NBS ⁱ Aromatic nitro/Aromatic amine Aromatic nitro, Hydrazine Aromatic amine, Alkyl aldehyde Acid halide Alkyl aldehyde Alkyl halide | ²⁰² |
| HMG CoA Reductase Inhibitor | 8 | 1 2 | Alkyl halide Acid halide | ²⁰³ |
| GW597599 | 6 | 1 3 | Acid halide Michael acceptor | ²⁰⁴ |
| Thymitaq | 7 | 1 2 3 4 5 | Aromatic amine, Hydroxylamine, Alkyl halide Oxime/Michael acceptor Michael acceptor, Peroxide Aromatic amine, Acid halide Michael acceptor | ²⁰⁵ |

¹⁹⁷Choy, A.; Colbry, N.; Huber, C.; Pamment, M.; *et al.*, *ibid*, **2008**, 12, 884-887.

¹⁹⁸Jiang, X.; Li, J.; Zhang, R.; Zhu, Y.; *et al.*, *ibid*, **2008**, 12, 888-891.

¹⁹⁹Gross, T.D.; Chou, S.; Bonneville, D.; Gross, R.S.; *et al.*, *ibid*, **2008**, 12, 929-939.

²⁰⁰Haycock-Lewandowski, S.J.; Wilder, A.; Åhman, J.; *ibid*, **2008**, 12, 1094-1103.

²⁰¹Åhman, J.; Birch, M.; Haycock-Lewandowski, S.J.; Long, J.; *et al.*, *ibid*, **2008**, 12, 1104-1113.

²⁰²Palmer, A.M.; Webel, M.; Scheulfer, C.; Haag, D.; *et al.*, *ibid*, **2008**, 12, 1170-1182.

²⁰³Bowles, D.M.; Bolton, G.L.; Boyles, D.C.; Curran, T.T.; *et al.*, *ibid*, **2008**, 12, 1183-1187.

²⁰⁴Guercio, G.; Bacchi, S.; Goodyear, M.; Carangio, A.; *et al.*, *ibid*, **2008**, 12, 1188-1194

²⁰⁵Malmgren, H.; Bäckström, B.; Sølver, E.; Wennerberg, J.; *et al.*, *ibid*, **2008**, 12, 1195-1200

| | | | | |
|--|----|---------------------------------------|---|----------------|
| | | 6 7 | Aromatic amine, hydrazine Pyrimidine analogue/Aromatic amine | |
| CCK 1R Receptor Agonist | 6 | 1 2 3 5 | Aromatic nitro/Michael acceptor Aromatic nitro, Acid halide Aromatic amine, Diazonium MSC | ²⁰⁶ |
| HIV Integrase Inhibitor | 10 | 2 3 4 6 7 8 9 10 | Hydroxylamine Michael acceptor Michael acceptor Pyrimidine analogue, MSC, Aromatic amine Sulfonate ester, Pyrimidine analogue Pyrimidine analogue Pyrimidine analogue Pyrimidine analogue, Acid halide | ²⁰⁷ |
| WAY-281418 | 6 | 1 2 3 4 5 6 | Alkyl sulfate ^j Acid halide Alkyl halide Acid halide Acid halide Hydroxylamine | ²⁰⁸ |
| 3-bromo-6-chloro-phenanthrene-9,10-dione | 6 | 1 3 5 6 | Acid halide Boronic acid Polyaromatic Polyaromatic/Alkyl halide, Polyaromatic/Michael acceptor | ²⁰⁹ |

(a).Crystallization/salt formation is counted as a single stage, (b). SSRI (Selective Serotonin Re-uptake Inhibitor), (c). TsCL (Tosyl Halide), (d). Reaction of HX with alcohol solvent, (e). Malic acid counter ion, (f). Reaction of nitric acid with alcohol solvent, (g). Side chain impurity, (h). MTA (methyl Tosic Acid), (i). NBS (N-Bromosuccinimide), (j). Reaction of sulfuric acid with alcohol solvent

²⁰⁶Kuethe, J.T.; Childers, K.G.; Humphrey, G.R.; Journet, M.; et al., *ibid*, **2008**, 12, 1201-1208.

²⁰⁷Zhong, Y-L.; Pipik, B.; Lee, J.; Kohmura, Y.; et al., *ibid*, **2008**, 12, 1245-1252.

²⁰⁸Wang, Y.; Papamichelakis, M.; Chew, W.; Sellstedt, J.; et al., *ibid*, **2008**, 12, 1253-1260.

²⁰⁹Limanto, J.; Dorner, B.T.; Hartner, F.W.; Tan, L.; *ibid*, **2008**, 12, 1269-1272.

**Table S-9: Summary of Reactive Intermediates Utilized in Multi-Stage Syntheses during 2009
(Reported in Organic Process R&D)**

| Drug Substance | No. of Synthetic stages ^a | Stage that Reactive Intermediate Introduced | Nature of Reactive intermediate | Reference |
|----------------------------------|--------------------------------------|---|--|----------------|
| Zafirlukast | 5 | 2 3 4 5 | Alkyl halide, Aromatic nitro Aromatic nitro Aromatic nitro Aromatic amine, Acid halide | ²¹⁰ |
| WAY-262398 | 8 | 7 | Alkyl aldehyde | ²¹¹ |
| Celecoxib | 1 | 1 | Hydrazine | ²¹² |
| LY518674 | 5 | 1 2 3 ^b 4 | Alkyl halide Acid halide Alkyl halide Aryl aldehyde, Isocyanate, Alkyl mesylate ^c Hydrazide | ²¹³ |
| CP-945598-01 | 5 | 1 2 3 4 5 | Aromatic amine, Aromatic amine, alkyl halide ^d Aromatic amine, Acid halide Alkyl sulfate ^e Purine analogue, Acid halide Purine analogue | ²¹⁴ |
| Aminoindanol -derived M1 agonist | 8 | 1 2 3 4 5 6 7 8 | Aromatic nitro Aromatic nitro Aromatic nitro, Peroxide Aromatic nitro/Peroxide Aromatic nitro Aromatic nitro, Acid halide Aromatic nitro Aromatic amine | ²¹⁵ |
| P38 MAP kinase inhibitor | 3 | 2 | Boronic acid derivative | ²¹⁶ |
| LY573636 | 4 | 1 2 | Acid halide Acid halide | ²¹⁷ |
| Eicosanoid pathway modulator | 8 | 1 2 3 4 | Acid halide Acid halide Alkyl halide Alkyl halide | ²¹⁸ |

²¹⁰Goverdhan, G.; Reddy, A.R.; Sampath, A.; Srinivas, K.; *et al.*, *ibid*, **2009**, 13, 67-72.

²⁰²Nikitenko, A.; Alimardanov, A.; Afragola, J.; Schmid, J.; *et al.*, *ibid*, **2009**, 13, 91-97.

²¹²Reddy, A.R.; Sampath, A.; Goverdhan, G.; Yakambararam, B.; *et al.*, *ibid*, **2009**, 13, 98-101.

²¹³Argentine, M.D.; Braden, T.M.; Czarnik, J.; Conder, E.W.; *et al.*, *ibid*, **2009**, 13, 131-143.

²¹⁴Ragan, J.A.; Bourassa, D.A.; Blunt, J.; Breen, D.; *et al.*, *ibid*, **2009**, 13, 186-197.

²¹⁵Hansen, M.M.; Borders, S.S.K.; Clayton, M.T.; Heath, P.C.; *et al.*, *ibid*, **2009**, 13, 198-208.

²¹⁶Thiel, O.R.; Achmatowitz, M.; Bernard, C.; Wheeler, P.; *et al.*, *ibid*, **2009**, 13, 230-241.

²¹⁷Yates, M.H.; Kallman, N.J.; Ley, C.P.; Wei, J.N.; *ibid*, **2009**, 13, 255-262.

²¹⁸Yates, M.H.; Koenig, T.M.; Kallman, N.J.; Ley, C.P.; *et al.*, *ibid*, **2009**, 13, 268-275.

| | | | | |
|---|----------------|------------------|---|----------------|
| | | 5 | Alkyl halide, Boronic acid | |
| Peroxisome proliferators activator receptor modulator | 5 | 1 2 | Alkyl halide Alkyl halide | ²¹⁹ |
| Sodelglitizar | 3 | 1 2 3 | Akyl halide, Acid halide, Chlorosulfonic acid Acid halide Alkyl halide | ²²⁰ |
| GSK376501 | 4 | 1 | Alkyl halide | ²²¹ |
| Corticotropin Releasing Factor (CRF) Antagonist | 4 | 1 2 3 | Hydrogen peroxide Aromatic N-oxide Aromatic N-oxide, Acid halide | ²²² |
| PHA-399733 | 9 ^c | 4 5 6 | MSC Sulfonate ester Alkyl halide | ²²³ |
| Naratriptan | 3 | 3 | Alkyl halide ^d | ²²⁴ |
| GW597599 | 6 | 1 3 4 | Acid halide Michael receptor Acid halide | ²²⁵ |
| BMS-561392 | 8 ^f | 4 6 8 | Alkyl halide Alkyl aldehyde Hydroxylamine, Alkyl halide ^d | ²²⁶ |
| Bradykinin 1 Antagonist | 4 | 1 2 3 4 | Aromatic amine Hydroxylamine Hydroxylamine Boronic acid | ²²⁷ |
| Selective PPAR γ modulator | 6 | 1 3 4 | Aromatic amine, Acid halide Acid halide Alkyl halide | ²²⁸ |
| (R)-tert-Bu ₄ -DOTAGA | 2 | 1 | Alkyl halide | ²²⁹ |
| Partial nicotinic acid agonist | 5 | 1 2 3 | Hydrazine Michael acceptor Michael acceptor, Acid halide | ²³⁰ |

²¹⁹Magnus, M.A.; Astelford, B.A.; Brennan, J.; Stout, J.R.; *et al.*, *ibid*, **2009**, *13*, 280-284.

²²⁰Brown, A.D.; Davis, R.D.; Fitzgerald, R.N.; Glover, B.N.; *et al.*, *ibid*, **2009**, *13*, 297-302.

²²¹Bullock, K.M.; Burton, D.; Corona, J.; Diederich, A.; *et al.*, *ibid*, **2009**, *13*, 303-309.

²²²Caron, S.; Do, N.M.; Sieser, J.E.; Whriteour, D.C.; *ibid*, **2009**, *13*, 324-330.

²²³Wuts, P.G.M.; Ashford, S.W.; Conway, B.; Havens, J.L.; *et al.*, *ibid*, **2009**, *13*, 331-335.

²²⁴Kumar, U.S.; Sankar, V.R.; Kumar, S.B.; Prabhu, M.P.; *et al.*, *ibid*, **2009**, *13*, 468-470.

²²⁵Guercio, G.; Manzo, A.M.; Goodyear, M.; Bacchi, S.; *et al.*, *ibid*, **2009**, *13*, 489-493.

²²⁶Savage, S.A.; Waltermire, R.E.; Campagna, S.; Bordawekar, S.; *et al.*, *ibid*, **2009**, *13*, 510-518.

²²⁷Menzel, K.; Machrouhi, F.; Bodenstein, M.; Aloreti, A.; *et al.*, *ibid*, **2009**, *13*, 519-524.

²²⁸Maligres, P.E.; Humphrey, G.R.; Marcoux, J-F.; Hillier, M.C.; *et al.*, *ibid*, **2009**, *13*, 525-534.

²²⁹Levy, S.G.; Jacques, V.; Zhou, K.L.; Kalogeropoulos, S.; *et al.*, *ibid*, **2009**, *13*, 535-542.

²³⁰Wilson, R.D.; Cleator, E.; Ashwood, M.S.; Bio, M.M.; *et al.*, *ibid*, **2009**, *13*, 543-547.

| | | | | |
|---|----|----------------|--|----------------|
| | | 4 | Michael acceptor, Acid halide, Diazonium | |
| Dopamine D ₂ partial agonist | 10 | 2 | Aromatic amine, Acid halide | ²³¹ |
| | | 4 | Aromatic aldehyde | |
| | | 5 | Aromatic aldehyde | |
| | | 7 | Aromatic amine, Isocyanate | |
| | | 10 | Alkyl aldehyde | |
| Roscovitine | 7 | 1 | Aryl aldehyde, Hydroxylamine | ²³² |
| | | 2 | Oxime | |
| | | 5 | Purine analogue | |
| | | 6 | Purine analogue | |
| | | 7 | Purine analogue | |
| Lacidipine | 2 | 1 | Michael acceptor, Aryl aldehyde (x2) | ²³³ |
| | | 2 | Michael acceptor/Aryl aldehyde, | |
| | | | Michael acceptor, Michael acceptor | |
| Ravuconazole | 10 | 4 | Acid halide | ²³⁴ |
| | | 5 | Epoxide | |
| | | 7 | Alkyl halide | |
| | | 8 | Epoxide | |
| | | 10 | Alkyl halide | |
| Pleuromutilin -derived antibiotic | 6 | 1 | Alkyl sulphate ^e | ²³⁵ |
| | | 3 | Acid halide | |
| | | 4 | Acid halide | |
| T-2639 | 5 | 1 | Aromatic aldehyde, Acid halide | ²³⁶ |
| | | 2 | Michael acceptor | |
| | | 3 | Michael acceptor, Alkyl halide | |
| | | 4 | Michael acceptor | |
| GSK812397 | 6 | 1 | Aromatic aldehyde | ²³⁷ |
| | | 3 | Michael acceptor | |
| | | 2 ^b | Aromatic amine, Alkyl halide | |
| | | 3 ^b | Aromatic aldehyde | |
| | | 4 | Aromatic aldehyde | |
| | | 6 | Formaldehyde | |
| Amine Hydrochloride Salts | 1 | 1 | Alkyl halide (x2) ^d | ²³⁸ |
| | | | | |
| Quetiapine | 4 | 1 | Acid halide, Aromatic amine | ²³⁹ |
| | | 3 | Alkyl halide | |
| | | 4 | Michael acceptor ^g | |
| Tentoprazole | 2 | 1 | Alkyl halide | ²⁴⁰ |

²³¹ Magano, J.; Acciaca, A.; Akin, A.; Collman, B.M.; *et al.*, *ibid*, **2009**, 13, 555-566.

²³² Oumata, N.; Ferandin, Y.; Meijer, L.; Galons, H.; *ibid*, **2009**, 13, 641-644.

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²³⁴ Pesti, J.; Chen, C.-K.; Spangler, L.; DelMonte, A.J.; *et al.*, *ibid*, **2009**, 13, 716-728.

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| | | | | |
|--|---------|----------------|--|----------------|
| | | 2 | Epoxide, Aryl N-oxide ^h | |
| SCP-123 | 2 | 1 | Aromatic amine, Acid halide/Alkyl halide | ²⁴¹ |
| | | 2 | Alkyl halide, Michael acceptor | |
| Progesterone receptor antagonist | 5 | 1 | Alkyl halide | ²⁴² |
| | | 3 | Hydrazine | |
| | | 4 | Alkyl halide | |
| WAY-315193 | 4 | 1 | Michael acceptor | ²⁴³ |
| | | 2 | Epoxide | |
| | | 3 | Epoxide | |
| | | 4 | TsCL ⁱ | |
| Rabeprazole | 3 | 1 | Alkyl halide | ²⁴⁴ |
| | | 3 | Aryl N-oxide ^h | |
| Denagliptan | 2 | 2 | Alkyl tosylate ^j | ²⁴⁵ |
| Ezetimibe | 8 | 1 | Acid halide | ²⁴⁶ |
| | | 5 | Acid halide | |
| | | 6 | Acid halide | |
| | | 7 | DMS ^k | |
| BCX-4208 | 7 | 1 | Hydroxylamine, Formaldehyde | ²⁴⁷ |
| | | 2 | Michael acceptor | |
| | | 7 | Purina analogue, Formaldehyde | |
| Cefozopran | 1 | 1 | Aromatic amine/ Michael acceptor/Acid halide, Aromatic amine/ Michael acceptor | ²⁴⁸ |
| Glycine antagonist | 9 CHECK | 1 | Acid halide | ²⁴⁹ |
| | | 2 | Michael acceptor | |
| | | 3 | Michael acceptor, Aromatic amine | |
| | | 4 | Michael acceptor | |
| | | 6 | Alkyl aldehyde | |
| | | 7 | Michael acceptor | |
| | | 8 | Michael acceptor | |
| | | 9 | Michael acceptor | |
| | | | | |
| ABT-279 | 7 CHECK | 5 | Acid halide, Acid halide | ²⁵⁰ |
| | | 6 | Acid halide | |
| | | 7 | Acid halide, Alkyl phosphate ^l | |
| | | 7 ^b | DBDMH ^m | |
| <i>N,N'</i> -Bis (4,6-disubstituted 1,3,5-triazin-2-yl)-4- | 7 | 1 | Aromatic amine (x2) | ²⁵¹ |
| | | 2 | Aromatic amine, TCT ⁿ | |
| | | 4 | Aromatic amine | |
| | | 5 | Aromatic amine | |
| | | | | |

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| | | | | |
|------------------------|---|------------------|---|-----|
| aminophenet ylamine | | 6 7 | Aromatic amine Aromatic amine (x2) | |
| Saxagliptin | 6 | 1 5 | Alkyl mesylate ^c Alkyl halide ^d | 252 |
| DG-051B | 6 | 1 2 5 6 | TsCl ⁱ Sulfonate ester Alkyl halide Alkyl halide ^d | 253 |
| Valsartan | 4 | 1 2 3 | Alkyl halide Acid halide Azide | 254 |
| Pioglitazone | 4 | 1 2 3 4 | TsCl ⁱ Sulfonate ester Aryl aldehyde Michael acceptor, Aryl aldehyde ^h | 255 |

(a).Crystallization/salt formation is counted as a single stage, (b). Side chain reaction, (c). Reaction of methanesulfonic acid with alcoholic solvent, (d). Reaction of HCl with alcohol solvent, (e). Reaction of sulfuric acid with alcohol solvent, (g) Salt forming agent, (h). Impurity in API, (i) TsCl (Tosyl chloride), (j). Reaction of tosic acid with alcohol solvent, (k). Dimethyl sulphide, (l). Reaction of phosphoric acid with alcohol solvent, (m) DBDMH (Dibromo dimethylhydantoin),(n). TCT (Trichlorotriazine)

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**Table S-10: Summary of Reactive Intermediates Utilized in Multi-Stage Syntheses during 2010
(Reported in Organic Process R&D)**

| Drug Substance | No. of Synthetic stages ^a | Stage that Reactive Intermediate Introduced | Nature of Reactive intermediate | Reference |
|-------------------------|--------------------------------------|---|--|----------------|
| CCR1 antagonist | 5 | 2 ^b 3 ^b 1 2 5 | Epoxide, Acid halide Epoxide Hydroxylamine, Acid halide Acid halide Epoxide | ²⁵⁶ |
| 5HT-4 receptor agonist | 7 | 1 4 6 7 | Acid halide NBS ^c Aromatic amine Aromatic amine (x2) | ²⁵⁷ |
| SB-406752 | 7 | 1 2 3 4 5 6 | Aromatic nitro Aromatic nitro Aromatic nitro Aromatic nitro Aromatic amine, NCS ^d Aromatic amine | ²⁵⁸ |
| BYK308944 | 7 | 1 3 4 5 | Aromatic nitro/Aromatic amine, Acid halide Aromatic nitro, Hydrazine Aromatic amine, Alkyl aldehyde Acid halide | ²⁵⁹ |
| Antibacterial macrolide | 3 | 1 2 3 | Azide Azide, Boronic acid Azide/Aromatic amine, Aromatic amine | ²⁶⁰ |
| BMS-561392 | 10 | 1 3 6 7 8 9 10 | Alkyl/Vinyl halide Alkyl aldehyde Hydroxylamine Hydroxylamine Aryl aldehyde Alkyl halide Hydroxylamine (x2) | ²⁶¹ |
| Rho-kinase inhibitor | 15 | 1 3 4 5 6 | Aromatic amine Epoxide Aromatic N-oxide Aromatic N-oxide/Aromatic nitro, Acid halide Aromatic nitro, Alkyl halide | ²⁶² |

²⁵⁶ Ainge, D.; Booker, J.E.M.; Pedge, N.; Sinclair, R.; *et al.*, *ibid*, **2010**, *14*, 72-84.

²⁵⁷ Walker, A.J.; Adolph, S.; Connell, R.B.; Laue, K.; *et al.*, *ibid*, **2010**, *14*, 85-91.

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²⁶¹ Magnus, N.A.; Campagna, S.; Confalone, P.N.; Savage, S.; *et al.*, *ibid*, **2010**, *14*, 159-167.

²⁶² Schirok, H.; Paulsen, H.; Kroh, W.; Chen, G.; *et al.*, *ibid*, **2010**, *14*, 168-173.

| | | | | |
|---|---|--------------------------------------|--|----------------|
| | | 7 8 9 12 15 | Aromatic nitro, Aromatic amine Aromatic amine Aromatic amine, Acid halide TsCL ^e Aromatic amine, Aromatic amine/Pyrimidine analogue, Aromatic amine | |
| Lanasoprazole | 2 | 1 2 | Alkyl halide Peroxide, Aryl N-oxide ^f | ²⁶³ |
| Muraglitazar | 4 | 1 2 3 4 | Acid halide Aromatic aldehyde Aromatic aldehyde Acid halide | ²⁶⁴ |
| Nolatrexed (Route A) | 5 | 1 2 3 4 5 | Peroxide Aromatic Amine Alkyl halide ^g Aromatic amine, Alkyl halide Aromatic amine/Pyrimidine analogue, Aromatic amine/Pyrimidine analogue | ²⁶⁵ |
| Amtolmetin | 8 | 1 2 3 4 5 6 7 8 | Acid halide Michael acceptor, Hydrazine DMS ^h Acid halide Michael acceptor Michael acceptor Michael acceptor Michael acceptor | ²⁶⁶ |
| Methoxytetra hydro-3-Benzazepines | 6 | 1 5 | Acid halide Acid halide/Alkyl halide | ²⁶⁷ |
| Diacyl glycerolacy ltransferase-1 inhibitor | 5 | 2 4 5 | Acid halide Aromatic nitro/Boronic acid, Alkyl halide Aromatic amine, Isocyanate | ²⁶⁸ |
| Next generation statin | 5 | 1 3 4 5 | Pyrimidine analogue Pyrimidine analogue Pyrimidine analogue, Aryl aldehyde Pyrimidine analogue, Aromatic amine, Alkyl halide Pyrimidine analogue (x2) | ²⁶⁹ |
| Ro4858542 | 6 | 1 2 | Aromatic nitro (x2) Aromatic nitro | ²⁷⁰ |

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| | | | | |
|---------------------|---|----------------------------|---|----------------|
| | | 3 4 5 6 | Aromatic amine, Acid halide DMS ^h Acid halide Alkyl halide ^g | |
| EDP-420 | 9 | 1 2 3 4 7 8 | Oxime Oxime Oxime Alkyl halide ^g DMS ^h , Isocyanate Hydroxylamine, Alkyl halide ^g | ²⁷¹ |
| Fulvestrant | 8 | 1 2 3 | Michael acceptor Michael acceptor, Alkyl halide Michael acceptor | ²⁷² |
| BMS-587101 | 5 | 1 2 3 4 | Isocyanate Aromatic aldehyde Michael receptor Acid halide | ²⁷³ |
| Ro5114436 | 8 | 1 4 6 | Michael acceptor, Alkyl aldehyde Acid halide Alkyl aldehyde | ²⁷⁴ |
| Etravirine | 3 | 1 3 | Aromatic amine Aromatic amine | ²⁷⁵ |
| Azaindole | 8 | 1 2 3 4 5 7 | Aromatic aldehyde, Azide Azide Methyl acrylate, Alkyl halide ^g Michael acceptor, Propenyl-stannane reagent Michael acceptor Acid halide | ²⁷⁶ |
| Casopitant Mesylate | 7 | 1 | Michael acceptor Acid Halide Mesylate ester ⁱ | ²⁷⁷ |
| FU-23 | 6 | 1 3 5 6 | Acid sulfate ^j Acid halide Boronic acid Boronic acid | ²⁷⁸ |
| GSK269984 | 6 | 2 3 4 | Alkyl halide Boronic acid Boronic acid, Alkyl halide | ²⁷⁹ |
| GV143253 | 6 | 1 2 | Alkyl halide Michael acceptor | ²⁸⁰ |

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| | | | | |
|--|----|----------------------------|--|----------------|
| | | 3 4 | Michael acceptor Michael acceptor | |
| c-MET kinase inhibitor | 5 | 1 2 4 5 | Alkyl halide Aromatic aldehyde Tricyclic halide Tricyclic halide, Boronic acid | ²⁸¹ |
| Imadazo-benzoxazine carboxamide derivative | 9 | 1 4 5 7 | Alkyl halide Alkyl aldehyde Alkyl halide Acid halide | ²⁸² |
| Alkylated dihydrobenzo-thiadiazole S,S-dioxide | 10 | 1 2 3 4 7 8 | Aromatic amine, Aromatic nitro Aromatic nitro Aromatic amine Acid halide Alkyl Azo Alkyl halide ^g | ²⁸³ |
| PDE-4 Inhibitor | 7 | 1 2 4 5 7 | Peroxide Aromatic N-oxide, Acid halide Aromatic amine, Boronic acid Aromatic amine, Diazonium Alkyl halide ^g | ²⁸⁴ |
| CRF-1 Antagonist | 7 | 1 2 3 4 5 | Aromatic amine, Alkyl halide/Acid Halide Alkyl halide Michael acceptor, Alky halide, Acid halide Michael acceptor Michael acceptor | ²⁸⁵ |
| GSK1360707 | 6 | 2 3 4 6 | Michael acceptor, Boronic acid Michael acceptor, Alkyl halide Alkyl halide Alkyl phosphonate ^k | ²⁸⁶ |
| 1-Benzhydryl-azetidin-3-ol | 2 | 1 | Epoxide/Alkyl halide | ²⁸⁷ |
| LFA-1/ICAM Inhibitor | 4 | 1 2 | Acid Halide Acid Halide | ²⁸⁸ |
| AZD0530 | 10 | 1 2 3 4 5 8 | Aromatic amine, Acid halide Michael acceptor, Peroxide Aromatic amine Aromatic amine Acid halide Aromatic amine | ²⁸⁹ |

²⁸¹ Stewart, G.W.; Brands, K.M.J.; Brewer, S.E.; Cowden, C.J.; *et al.*, *ibid*, **2010**, *14*, 849-858.

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| | | | | |
|-----------------------------|----------------|----------------------------|---|----------------|
| | | 10 | Alkyl aldehyde | |
| AZD0530 | 8 | 2 3 5 | Acid halide Aromatic amine Alkyl halide ^g | ²⁹⁰ |
| Peptide-like Diabetes drug | 9 ^l | 1 2 3 4 8 | Aromatic nitro/aromatic aldehyde Aromatic nitro Aromatic nitro, MsCl ^l Sulfonate ester/Aromatic nitro Polyaromatic ^m | ²⁹¹ |
| Pramipexole | 5 | 1 2 3 4 5 | Thiourea Aromatic amine Aromatic amine Aromatic amine Aromatic amine, Aromatic amine | ²⁹² |
| GSK356278 | 7 | 1 3 4 5 6 7 | Aromatic amine, Michael acceptor, Acid halide Alkyl halide ^g Hydrazine Hydrazide Hydrazine Hydrazide | ²⁹³ |
| KW-4490 | 6 | 1 | NBS ^c , Alkyl halide | ²⁹⁴ |
| Tenovir Disoproxil Fumarate | 4 CHECK | 1 2 3 4 | Purine/Aromatic amine Purine analogue/Aromatic amine, Phosphonate ester Purine analogue/Aromatic amine /Phosphonate ester Purine analogue/Aromatic amine /Phosphonate ester (x2), Alkyl halide, Michael acceptor | ²⁹⁵ |
| BMS-764459 | 7 | 1 2 3 4 5 6 | Aromatic nitro, Acid halide Aromatic nitro Aromatic nitro Aromatic nitro/Michael acceptor, FSA ⁿ Aromatic nitro Aromatic amine, Michael acceptor | ²⁹⁶ |
| Orexin receptor antagonist | 9 | 1 2 4 6 | Alkyl halide TBDPSCI ^o , alkyl halide Alkyl halide Alkyl aldehyde | ²⁹⁷ |
| GSK923295A | 10 | 4 | NBS ^c | ²⁹⁸ |

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²⁹⁸ Bellingham, R.; Buswell, A.M.; Choudray, B.M.; Gordon, A.H.; et al., *ibid*, **2010**, *14*, 1254-1263.

| | | | | |
|--|----|---|--|----------------|
| | | 5 6 8 | Alkyl halide, Aromatic amine Acid halide Hydrazine | |
| β-3 Adrenergic Receptor Antagonist | 8 | 3 | Alkyl halide ^g | ²⁹⁹ |
| Antibacterial macrolone | 13 | 1 2 3 4 5 6 7 8 9 10 11 12 13 | Acid halide Acid halide, Michael acceptor Michael acceptor | ³⁰⁰ |
| 5-HT _{2c} receptor antagonist | 11 | 1 3 5 6 7 8 9 | Boronic acid Alkyl halide Peroxide TsCl ^e Sulfonate ester, Diazonium compound Diazonium compound Alkyl halide | ³⁰¹ |
| Fexofenadine | 6 | 1 3 4 5 | DMS ^b Michael acceptor TSCl ^e Alkyl halide, | ³⁰² |

(a).Crystallization/salt formation is counted as a single stage, (b). Side chain, (c). NBS (*N*-Bromosuccinimide), (d). NCS (*N*-Chlorosuccinimide), (e). TsCl (Tosyl chloride), (f). Impurities, (g). Reaction of HCl with alcohol solvent, (h). DMS (dimethylsulfate), (i). mesylate esters, (j). Reaction of sulphuric acid with alcohol solvent, (k). Reaction of H₃PO₄ with alcohol solvent, (l). Impurity in main intermediate, (m). MsCl (Mesyl chloride), (n). FSA (2-(flurosulfonyl)acetic acid, (o). TBDPSCl (*tert*-butylchlorodiphenylsilane).

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