Synthetic Approaches to the 2004 New Drugs

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Abstract: New drugs are introduced to the market every year and each individual drug represents a privileged structure for its biological target. In addition, these new chemical entities (NCEs) not only provide insights into molecular recognition, but also serve as leads for designing future drugs. To this end, this review covers the syntheses of 12 NCEs marketed in 2004.

Keywords: Synthesis, New Drug, New Chemical Entities.

INTRODUCTION

"*The most fruitful basis for the discovery of a new drug is to start with an old drug*." — Sir James Whyte Black, winner of the 1998 Nobel prize in physiology and medicine [1].

Inaugurated two years ago, this annual review presents synthetic methods for molecular entities that were launched in various countries for the first time during the past year. The motivation to write such a review is the same as stated in the previous article[2-3]. Briefly, drugs that are approved worldwide tend to have structural similarity across similar biological targets. We strongly believe that knowledge of new chemical entities and their syntheses will facilitate our ability to design new drug candidates.

In 2004, 23 NCEs including biological drugs, and two diagnostic agents [4] reached the market. Among them, some products were approved for the first time in 2004 but were not launched before year end. The synthesis of those drugs will be covered in the next review. The current article will focus on the syntheses of the 11 new drugs and one diagnostic agent (gadoxetic disodium) marketed last year (Fig. **1**), but excludes new indications for known drugs, new combinations and new formulations. Drugs synthesized *via* bio-process and peptide synthesizers will also be excluded as well. Syntheses of these new drugs were published sporadically in different journals and patents. The synthetic routes cited here represent the most scalable methods based on the authors' judgment on available publications and appear in alphabetical order by generic names.

Azacitidine (*Vidaza*™)

Azacitidine, an inhibitor of DNA methyltransferase, was approved by the US FDA for the treatment of myelodysplastic syndromes in May, 2004 [4]. It is the first drug to be approved by the FDA for treating this rare family bone-marrow disorders, and has been given orphan-drug status. It is also a pioneering example of an agent that targets "epigenetic" gene silencing, a mechanism that is exploited by cancer cells to inhibit the expression of genes that counteract the malignant phenotype [5]. The triazine ring of azacitidine is sensitive to water [6]; this characteristic has made the synthesis of azacitidine a challenge, especially in manufacturing at commercial scale. A number of reports have appeared in order to avoid the use of water; however, these methods all have additional problems that render them undesirable for the large scale synthesis [7-12]. A recent improved synthesis [13] is depicted in Scheme **1**. 5-Azacytosine (**1**) was bis-silylated with HMDS in the presence of $(NH_4)SO_4$ to furnish trimethylsilylated azacytosine (**2**) in greater than 90% yield. Coupling of silylated azacytosine **2** with 1,2,3,5-*tetra*-*O*-acetyl-β-*D*-ribofuranose (**3**) in DCM in the presence of TMS-triflate provided protected 5-azacitidine **4**. The acetyl groups were then removed by using NaOMe in MeOH at rt. The crude azacitidine was crystallized from DMSO/MeOH to provide pure azacitidine (**I**).

Belotecan Hydrochloride (*Camtobell*®)

The DNA topoisomerase I inhibitor, belotecan hydrochloride (**II**), developed by Chong Kun Dang Pharmaceuticals, was launched for the first time last year in the Republic of Korea as an injectable formulation, where it is indicated for the treatment of non-small-cell lung cancer as well as ovarian cancer. The initial discovery synthetic route involved over 12 steps. The large scale synthesis was developed later [14-15]. Treatment of commercially available camptothecin (**5**) with *tert*-butylhydroperoxide in the presence of $FeSO_4$, AcOH and conc. H_2SO_4 gave (*S*)-7-methylcamptothecin (**6**). Mannich reaction of compound **6** with isopropylamine hydrochloride in DMSO as a formaldehyde source gave belotecan hydrochloride (**II**).

The total synthesis route is depicted in Scheme **2.2**. The known pyridinone **7** [16] was converted to the bicyclic pyridinone **8** by treatment with methyl acrylate and K_2CO_3 in DMF. Hydrolysis and decarboxylation of **8** to ketone **9** was effected by refluxing in a mixture of HOAc and conc. HCl under nitrogen. Ketalization was performed in a two phase system of toluene and ethylene glycol to provide ketal **10** in 90% yield. Functionalization of the methyl group in **10** using diethyl carbonate in the presence of KH furnished the ester **11** in 76% yield. Ethylation of **11** was accomplished by use of $KOBu^t$ and EtI in DME. Catalytic hydrogenation of **12** using Raney Ni in a mixture of Ac_2O and HOAc gave the amide **13**. Removal of the catalyst by filtration followed by addition of $NaNO_2$ to the filtrate gave the *N*-nitroso amide. Decomposition of the nitroso amide by

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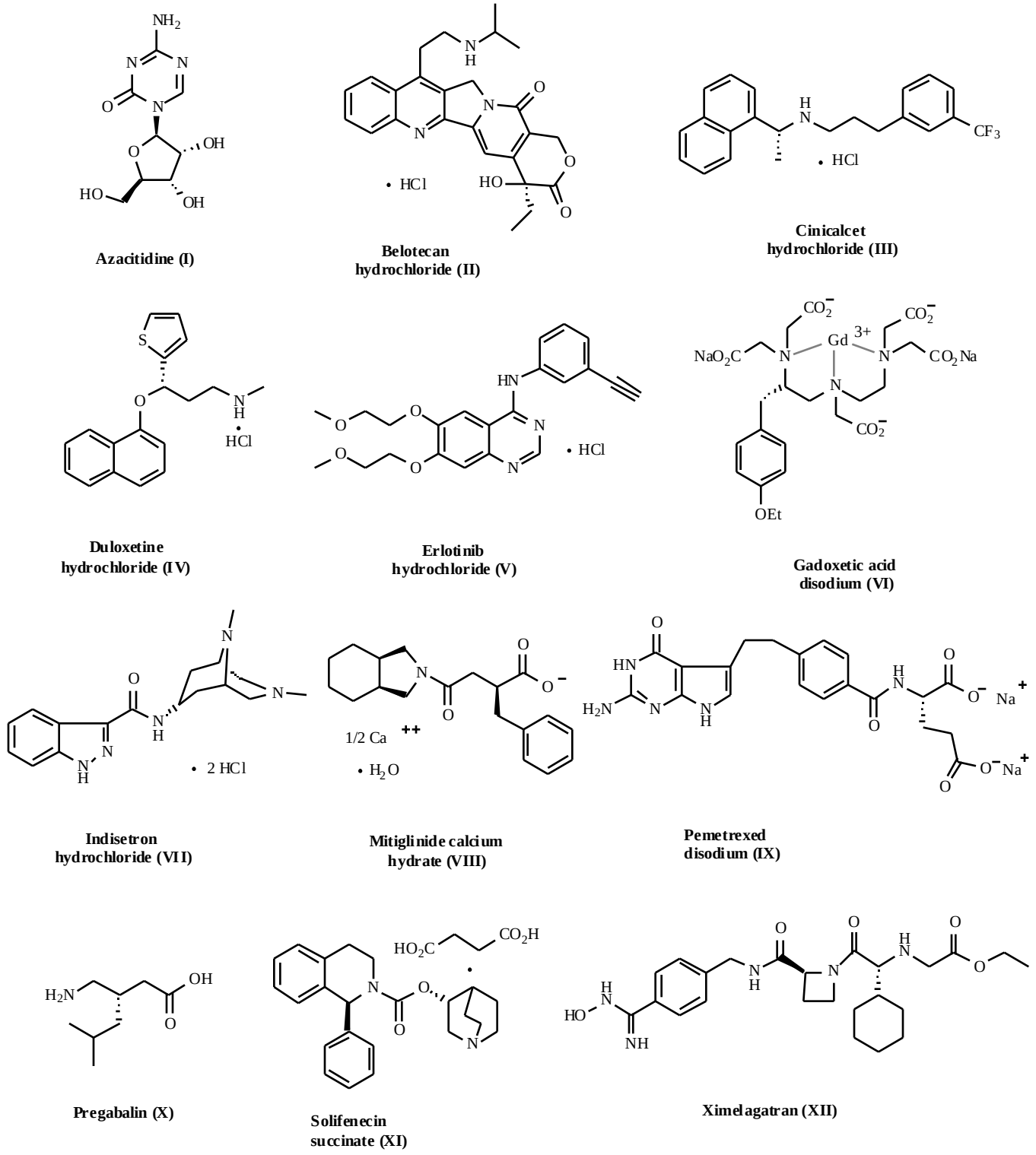
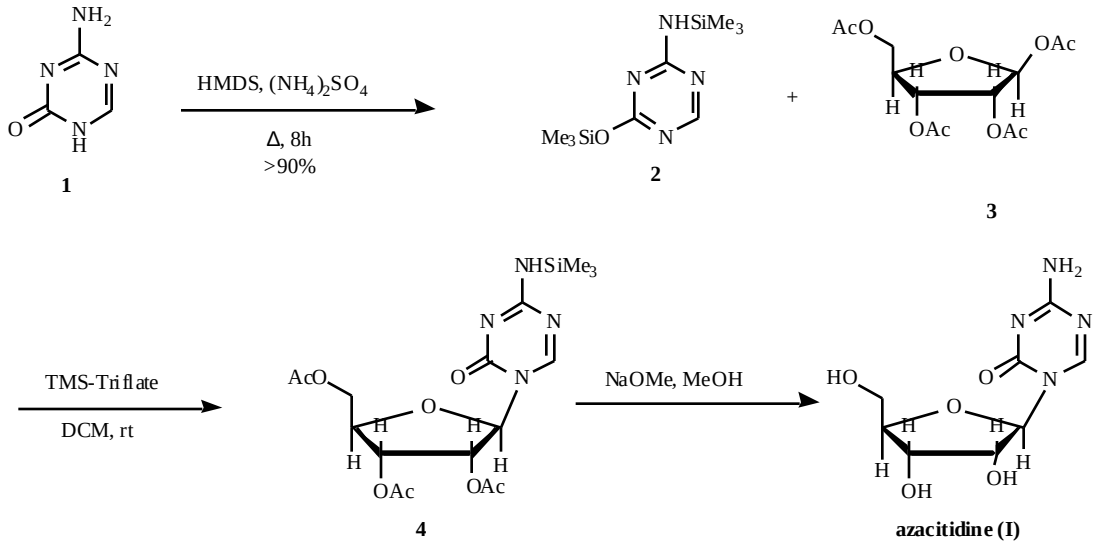


Fig. (1). Structures of 12 NCEs marketed in 2004.

heating in an inert solvent (CCl_4) gave the acetate **14** [17]. The diester **14** was lactonized by LiOH in MeOH/H_2O to give lactone **15** in 92% yield [18]. The carbonyl group in **15** was then reduced with DIBAL-H in THF to give lactol, which was dehydrated *via* its mesylate to afford **16** [19]. The asymmetric dihydroxylation of **16** gave diasteromeric mixtures in favor of the desired isomer **17** (81% d.e.). Compound **16** was then oxidized directly with iodine in the presence of $CaCO_3$ to give α-hydroxy lactone **18**. The deketalization was accomplished by HCl in THF/H_2O to provide the ketone **19** [19]. Condensation of ketone **19** and the amine **20** [20] in the presence of *p*-TSA followed by hydrolytic removal of Cbz group provided the free base Which was convert to its corresponding HCl salt as belotecan hydrochloride (**II**).



Scheme 1. Synthesis of azacitidine (**I**).

Cinacalcet Hydrochloride (*Sensipar* ™, *Mimpara*®)

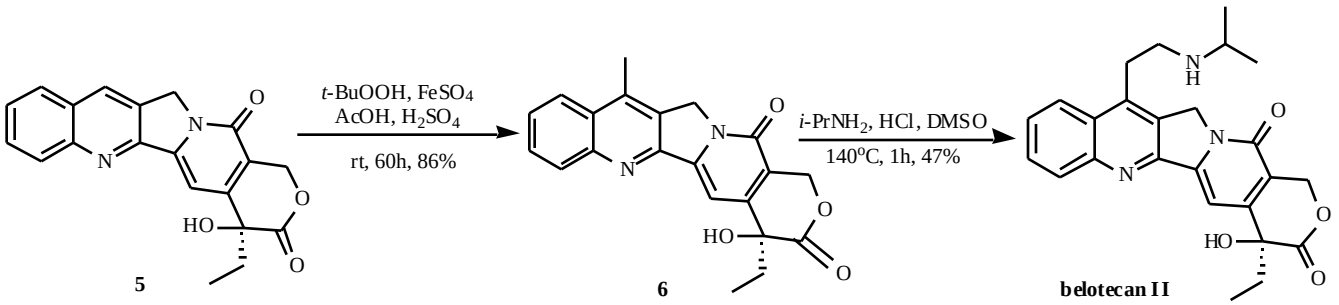
Amgen's cinacalcet (**III**) was licensed from NPS Pharmaceuticals as a first-in-class oral calcimimetic for the treatment of secondary hyperparathyroidism (HPT) in chronic kidney disease patients on dialysis and the treatment of hypercalcemia in patients with parathyroid carcinoma [21]. Cinacalcet's (**III**) mechanism of action is *via* inhibition at an allosteric site on the calcium-sensing receptor. The drug increases the sensitivity of the calcium receptor in the parathyroid gland to extracellular calcium and thereby reduces the levels of parathyroid hormone [22]. General syntheses of this class of compounds have been published [23], however, the specific synthesis of cinacalcet (**III**) has not been available to date. The synthesis of cinacalcet, based on a patented procedure, is depicted in Scheme **3**. A mixture of 1-acetonaphthone (**21**), 3-trifluoromethyl-1-propylamine (**22**) and titanium (IV) isopropoxide were stirred at rt to form the enamine intermediate which was reduced with methanolic sodium cyanoborohydride at rt to give corresponding racemic α-methyl amine (**23**). Compound **23** was resolved and then treated with HCl etherate to give cinacalcet hydrochloride (**III**) as a white solid.

Duloxetine Hydrochloride (*Cymbalta*™, *Yentreve*®/ *Ariclaim*®)

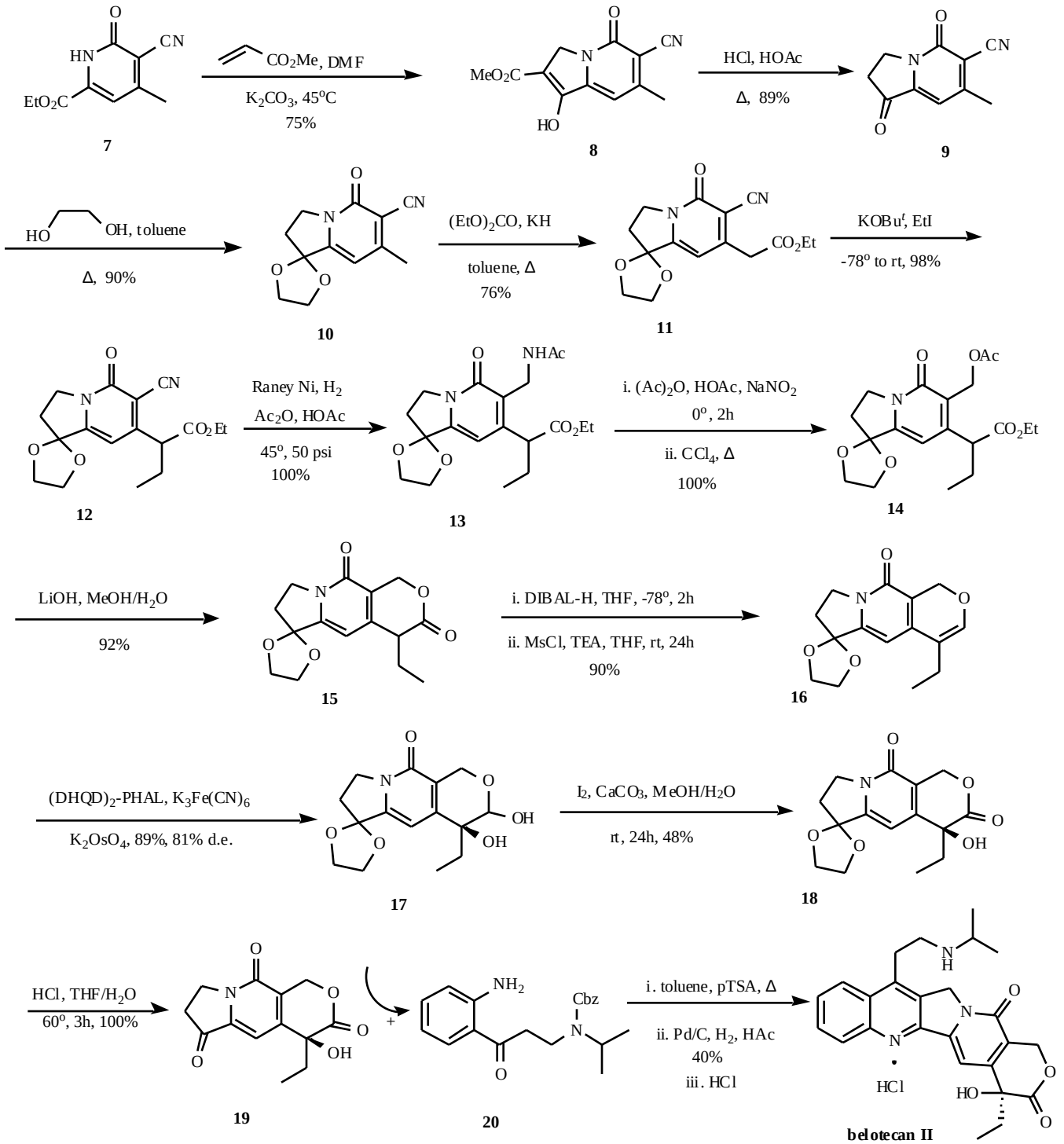
Lilly, in collaboration with Boehringer Ingelheim and Shionogi, has developed and launched duloxetine (**IV**), an orally active dual norepinephrine (NE) and serotonin reuptake inhibitor, as a treatment for depression [24] and urinary incontinence [25]. The balanced dual NE and serotonin reuptake inhibitor increases neurotransmitter concentration, which is believed to enhance the tone and contraction of the urethral sphincter and help to prevent accidental urine leakage due to physical activity . The synthesis from Lilly's group [26] is depicted in Scheme **4**. Friedel-Crafts acylation of thiophene (**24**) by 3-chloropropanoyl chloride (**25**) with $SnCl_4$ as Lewis acid gave ketone **26** which was then enantioselectively reduced with (*R*)-1-methyl-3,3-diphenyl-tetrahydropyrrolo[1,2-c][1,3,2]oxazaborole (**27**) in the presence of borane in THF to give (*S*)-3-chloro-1-(2-thienyl)-1-propanol (**28**). Compound **28** was subjected to Finkelstein reaction to give (*S*)-3-iodio-1-(2-thienyl)-1-propanol which was reacted with methylamine in THF to give compound **29**. The alcohol **29** was then used in a nucleophilic displacement reaction with 1-fluoronaphthalene (**30**) in the presence of sodium hydride in DMA to give duloxetine free base in 88% yield. Finally, the free base was treated with HCl to yield duloxetine hydrochloride (**IV**).

Erlotinib Hydrochloride (*Tarceva*™)

Erlotinib hydrochloride (**V**), a quinazoline derived small molecule inhibitor of epidermal growth factor receptor (EDGFR) tyrosine kinase, was approved in November, 2004, for the treatment of advanced or metastatic non-small-cell lung cancer [4]. It belongs to the same class as gefitinib,

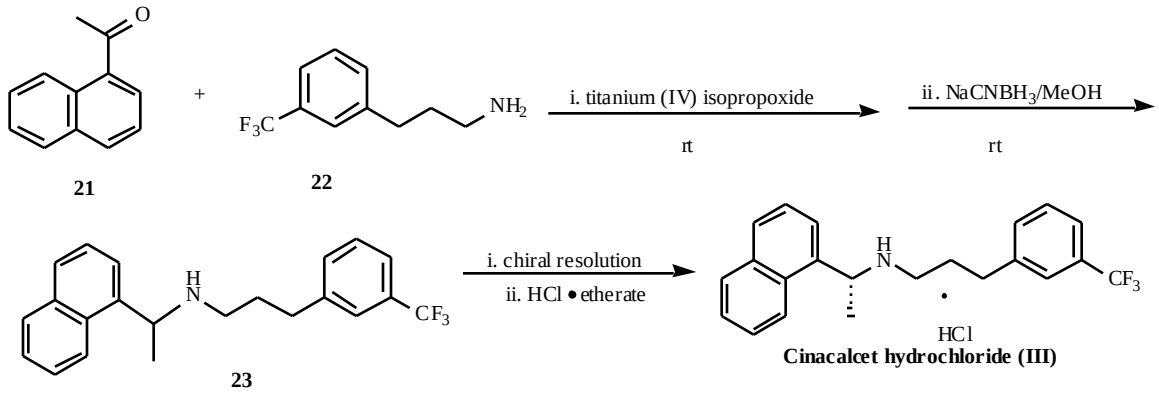


Scheme 2.1. Synthesis of belotecan hydrochloride (**II**).

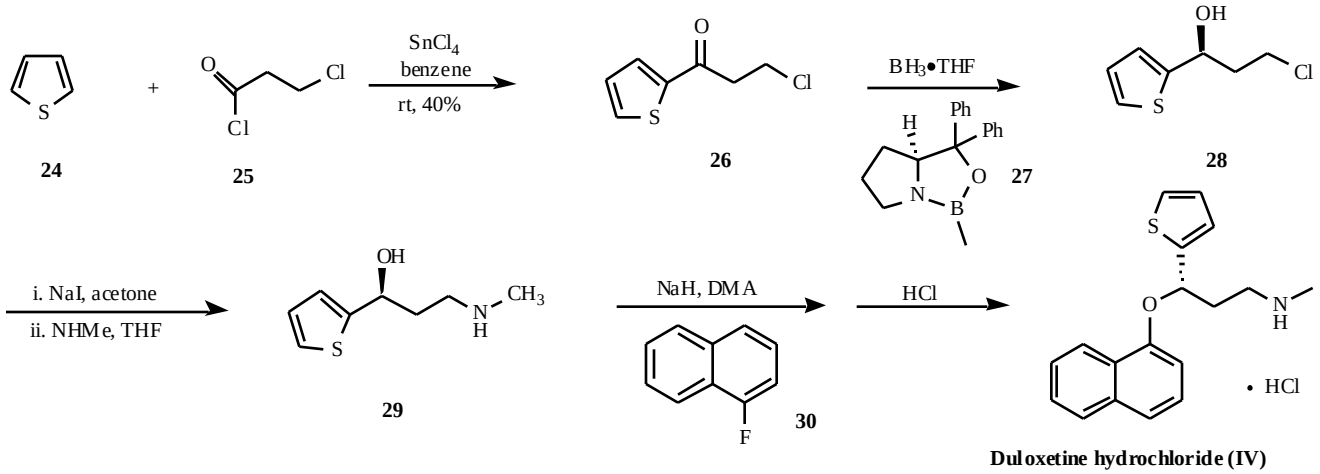


Scheme 2.2. Total Synthesis of belotecan hydrochloride (**II**).

another quinazoline approved for treatment of advanced lung cancer, but with improved pharmacokinetic properties [27-28]. The molecule was originated by Pfizer and development initiated in collaboration with OSI, which assumed full rights to the drug when Pfizer merged with Warner Lambert. Subsequently, Genentech/Roche went into licensing agreement with OSI to develop and market the drug in the US and Worldwide [29]. The synthesis of this agent is based on the original patent and is shown in Scheme **5** [30-32]. The 3,4-dihydroxy benzoate **31** was reacted with bromoethyl methyl ether in the presence of potassium carbonate and tetrabutyl ammonium iodide to give **32** in 93% yield. Nitration followed by hydrogenation provided **34** in 88% yield, which was then cyclized in formamide with ammonium formate to provide quinazolone **35.** . Subsequent reaction with oxalyl chloride gave quinazoline chloride **36**, which was then reacted with 3-ethynyl aniline (**37**) in isopropanol in the presence of pyridine to give the desired product erlotinib, which was isolated as the HCl salt (**V**). An alternate synthesis, that used protected 3-trimethylsilyl ethynyl aniline to couple to the quinazoline chloride **36**, has also been published [32].



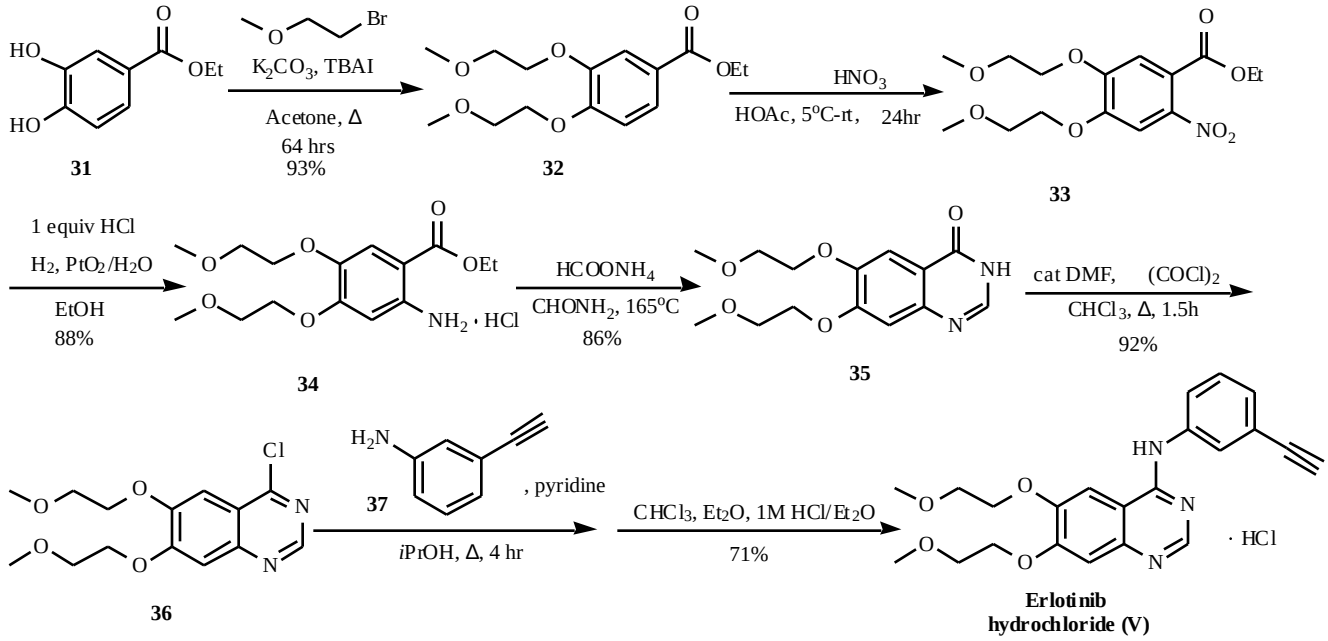
Scheme 3. Synthesis of cinacalcet hydrochloride (**III**).



Scheme 4. Synthesis of duloxetine hydrochloride (**IV**).

Gadoxate Disodium (*Primovist*®)

Schering AG's liver imaging product , gadoxate disodium (**VI**) was approved and launched last year in Sweden. Gadoxate is designed for the detection and characterization of liver lesions. Owing to its structural properties, gadoxate is specifically taken up by the hepatocytes, so that lesions with no or minimum hepatocyte

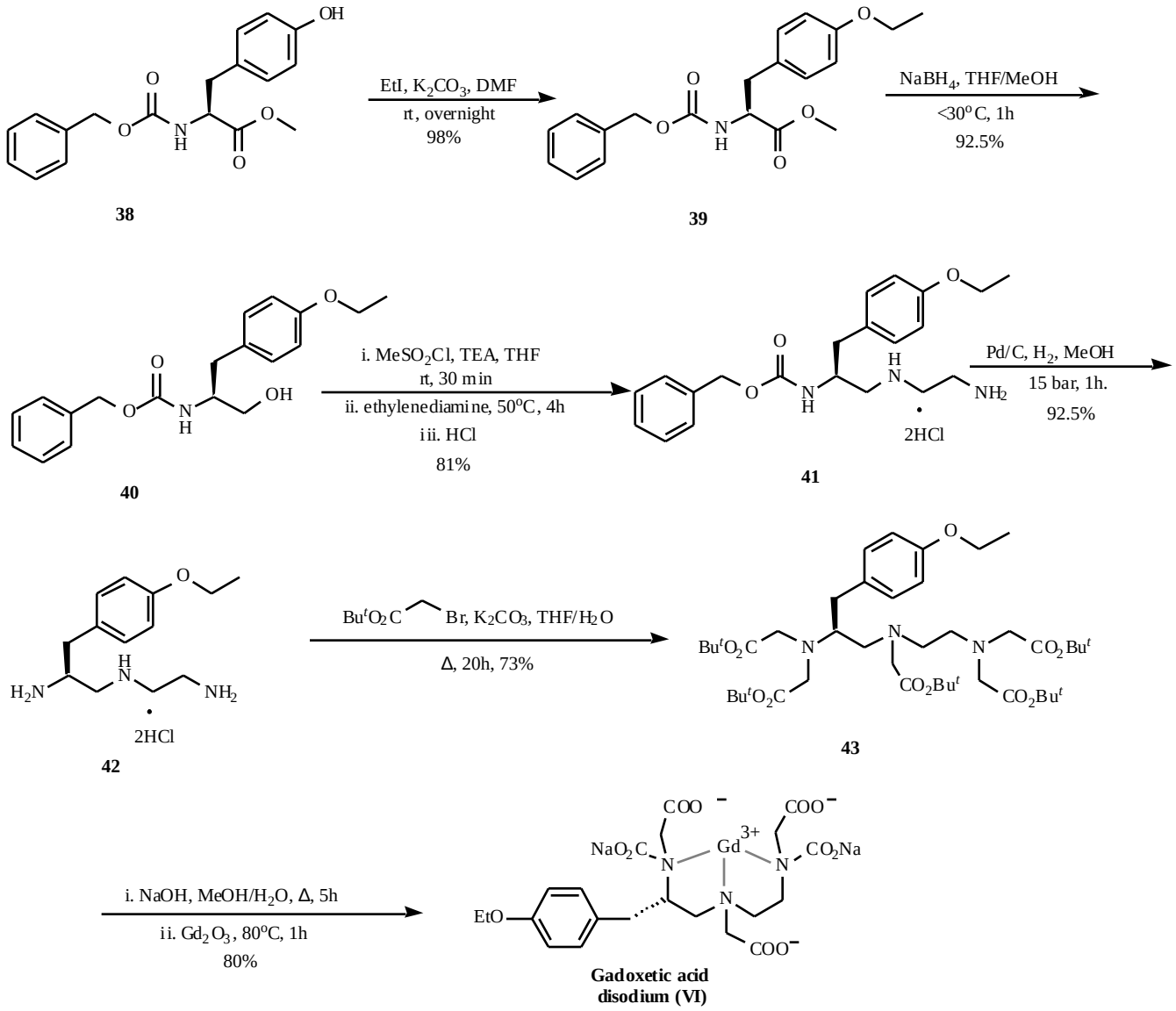


Scheme 5. Synthesis of erlotinib hydrochloride (**V**).

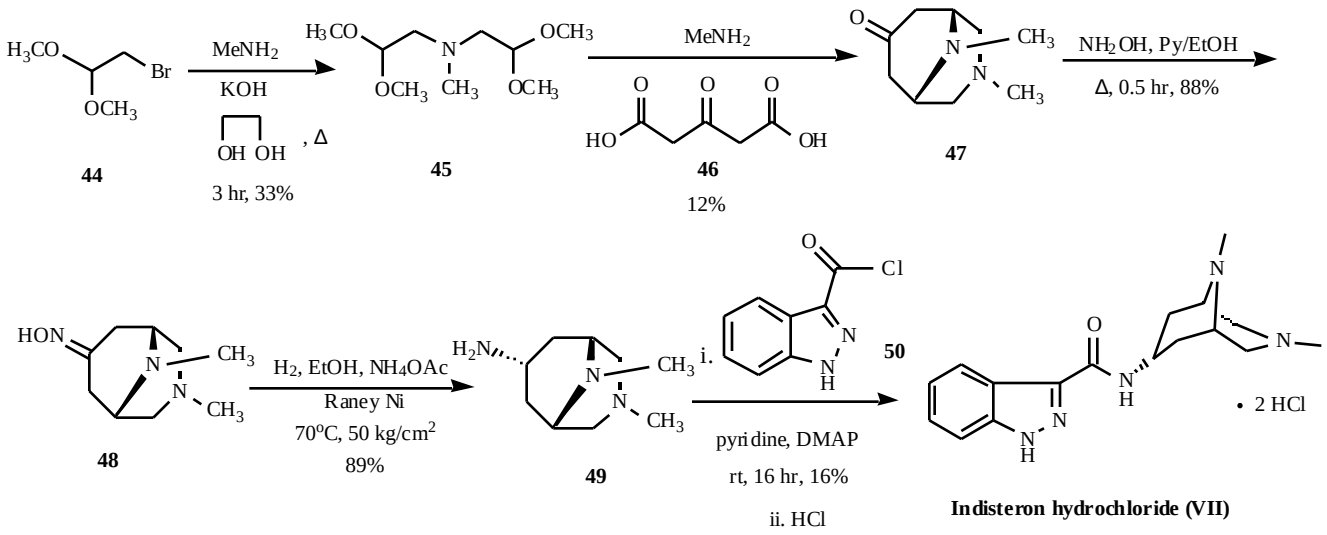
function remain un-enhanced and are therefore more readily detected and localized [33-35]. A scalable synthesis of gadoxate (**VI**) has appeared [36] (Scheme **6**). The commercially available N_a-benzyloxy-carbonyl-*L*-tyrosine methyl ester (**38**) was *O*-alkylated at the phenolic hydroxyl group with ethyl iodide in DMF to yield the ethyl ether **39** in 98% yield. Ester **39** was reduced to corresponding alcohol **40** using sodium borohydride in MeOH. Mesylation of **40** and further reaction with excess of ethylendiamine and addition of aqueous HCl afforded the mono-protected triamine dihydrochloride **41** in 81% yield. Catalytic hydrogenation afforded chiral triamine **42** as the dihydrochloride salt in 93% yield. Triamine **42** was then treated with *t*-butyl bromoacetate in THF/H_2O using K_2CO_3 as a base. The resulting crude product was subjected to preparative chromatography on reverse-phase silica gel yielding the oily *penta-t*-butyl ester **43** in 73% yield. The *penta-t*-butyl ester **43** was then hydrolyzed by sodium hydroxide. After cleavage of the *t*-butyl groups, the excess of sodium ions was removed by addition of cation-exchange resin Amberlite IR 120 to yield the sodium salt, which was then reacted with Ga_2O_3 in water at 80˚C to give gadoxetic acid disodium (**VI**) after neutralization with NaOH.

Indisetron Hydrochloride (*Sinseron*^{TM})

Indisetron is a dual serotonin $5HT_3/5HT_4$ receptor antagonist co-developed by Nisshin Pharma and Kyorin. It was approved for the first time in Japan for the treatment of prophylaxis of chemotherapy-induced nausea and vomiting [37]. The synthesis [38-39] is highlighted in Scheme **7**. Bromoacetaldehyde dimethyl acetal (**44**) was condensed with methylamine with KOH in refluxing ethyleneglycol for 3 hr to give 33% yield of bis(2,2-dimethoxyethyl)amine (**45**), which was cyclized with acetonedicarboxylic acid (**46**) and methylamine to generate 3,9-dimethyl-3,9-diazabicyclo-[3.3.1]nonan-7-one (**47**) in 12% yield. Compound **47** was reacted with hydroxylamine in refluxing pyridine and ethanol mixture to give corresponding oxime **48** in 88% yield, which was subsequently reduced with hydrogen over Raney Ni in hot ethanol in the presence of ammonium acetate at 50 kg/cm^2 to give amine **49** in 89% yield. Compound **49** was



Scheme 6. Synthesis of gadoxate disodium (**VI**).

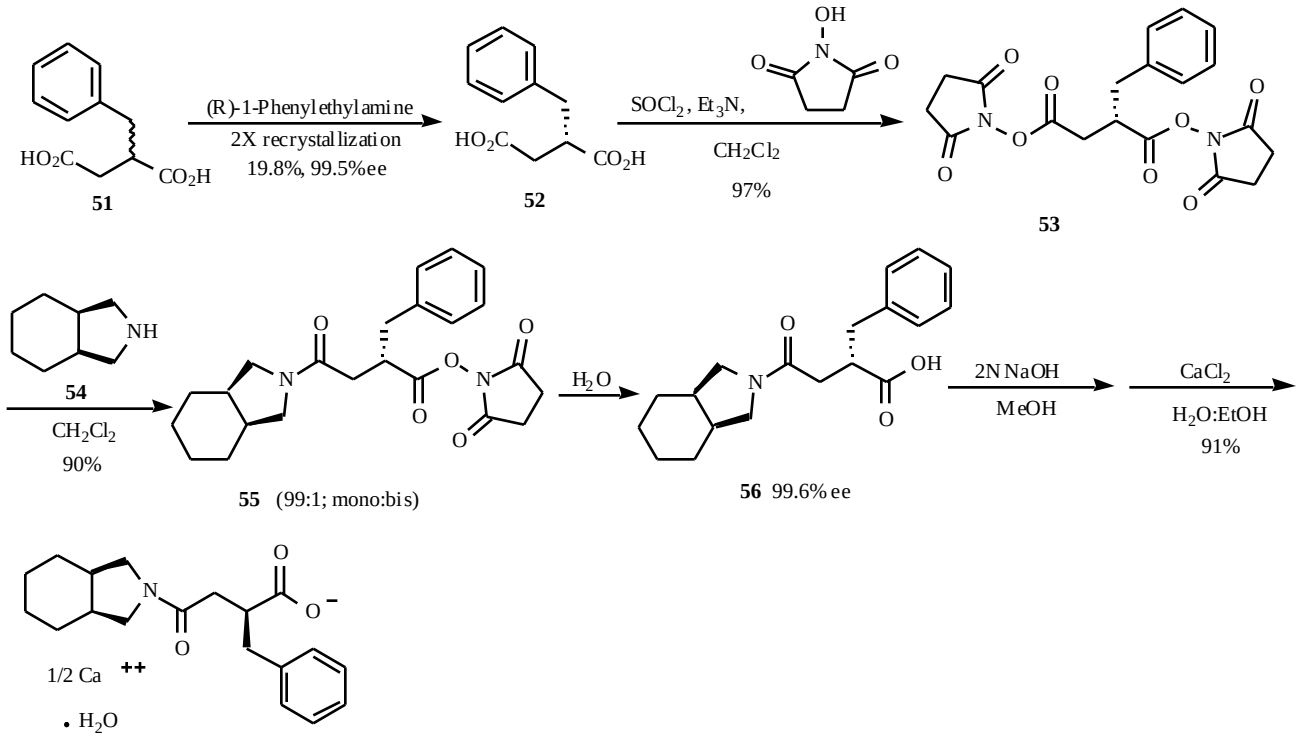


Scheme 7. Synthesis of indisteron hydrochloride (**VII**).

condensed with 1H-indazole-3-carbonyl chloride (**50**) in pyridine with catalytic amount of DMAP to give crude indisteron free base, which was re-crystallized from chloroform/hexane to give indisteron free base as colorless crystals in 16% yield. Finally, the free base was treated with hydrogen chloride to give indisteron hydrochloride (**VII**).

Mitiglinide Calcium Hydrate (*Glufast* ®)

Mitiglinide, an insulin secretagogue developed by Kissei and co-marketed by Kissei and Takeda, was approved for the treatment of type 2 diabetes in Japan in May of 2004 [4]. This secretagogue works by inhibiting ATP dependent influx of potassium in pancreatic beta cells, which induces depolarization of the cell and opens voltage dependent calcium channels that increases calcium levels in beta-cells and results in insulin release. A number of publications and patents have disclosed the syntheses of mitiglinide [40-44]. One of the syntheses describing the preparation of mitiglinide using bis-activated esters to obtain a selective mono amide is described in Scheme **8**. The synthesis starts with racemic 2-benzylsuccinic acid (**51**) which was resolved

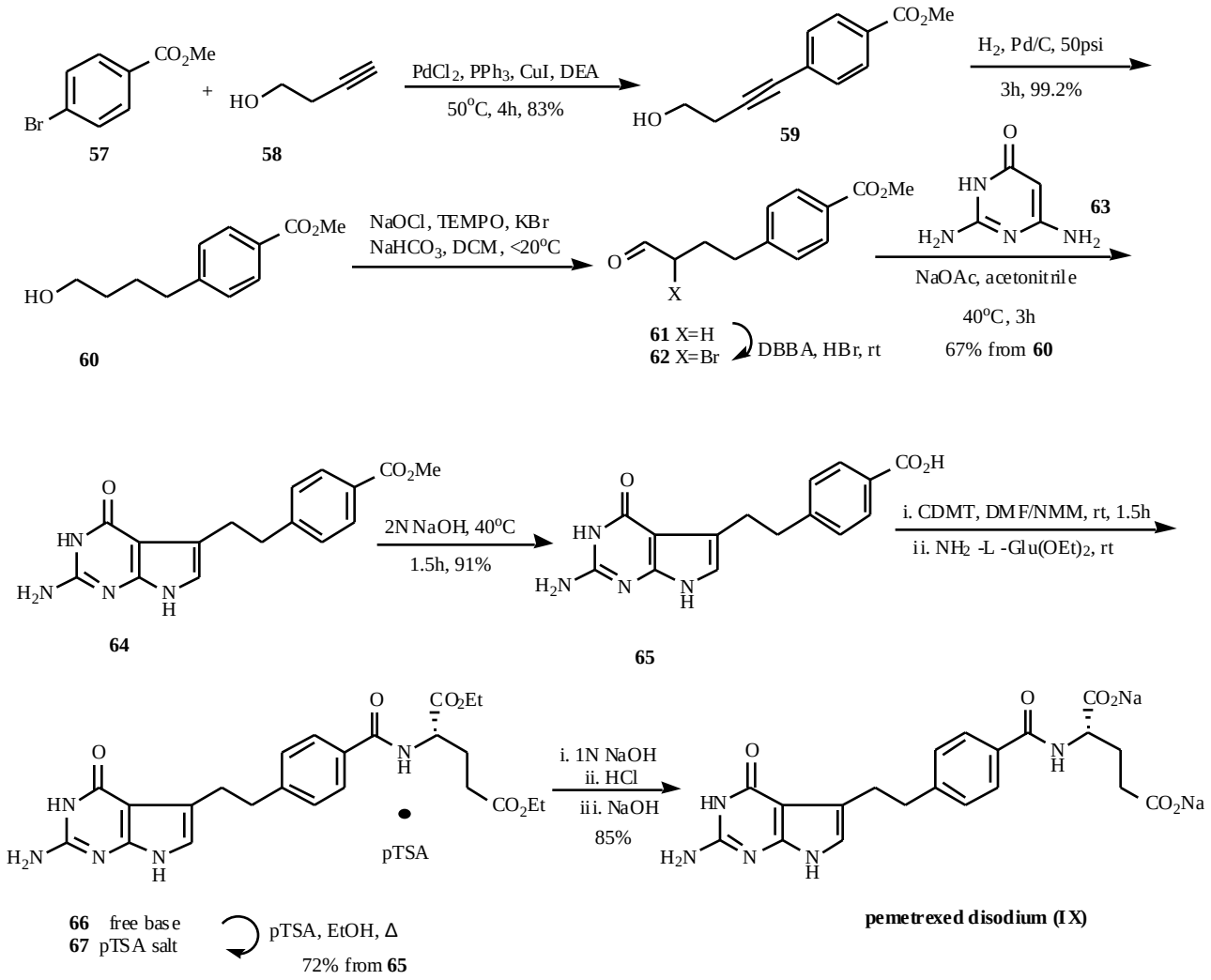


Scheme 8. Synthesis of mitiglinide calcium hydrate (**VIII**).

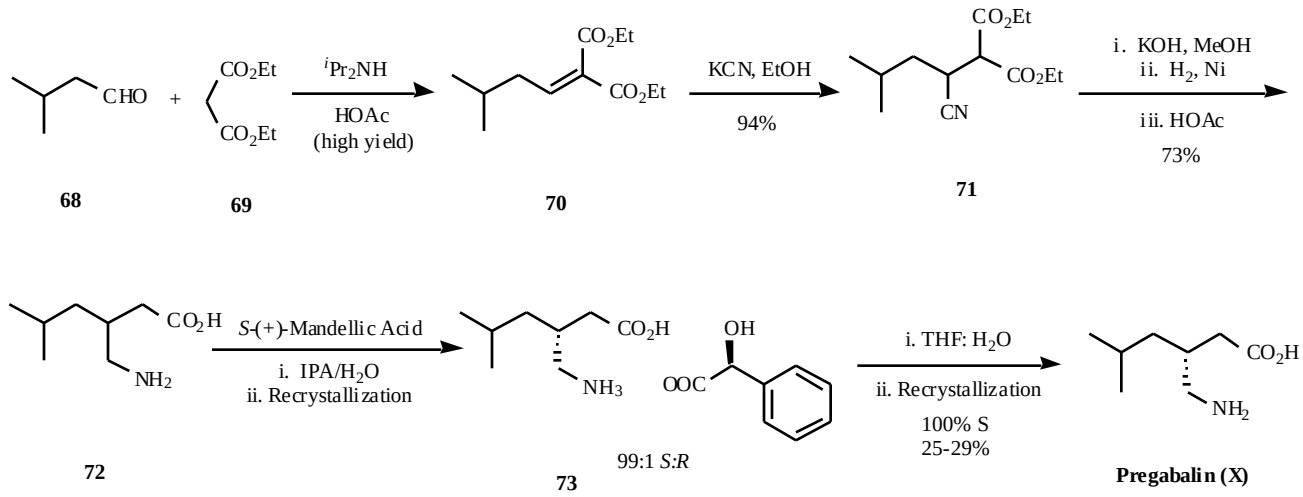
into its enantiomer using chiral amine salt formation and crystallization. Out of several amines used, (*R*)-1-phenylethylamine gave the best results for the chiral resolution (99.5% ee, 19.5%). Acid **52** was treated with thionyl chloride and triethylamine followed by *N*-hydroxysuccinamide to give doubly activated ester **53** (97%). Treatment of this double ester **53** with tetrahydroisoindoline (**54**) [45] gave selectively mono amide to di-amide in 99:1 ratio. Hydrolysis of the activated ester in **55** with water gave desired product **56** in 99% yield. Subsequent conversion in two steps to the half calcium salt provided mitiglinide calcium hydrate (**VIII**) in 91% yield.

Pemetrexed Disodium (*Alimta*®)

Pemetrexed is a novel multi-targeting antifolate that simultaneously blocks at least three separate enzymes essential to the survival of cancer cells: thymidylate synthase, dihydrofolate reductase and glycinamide ribonucleotide formyltransferase. Pemetrexed is broadly active in wide variety of solid tumors, including mesothelioma, non-small cell lung cancer, breast, bladder, head and neck, and ovarian cancers. A number of papers outlining the syntheses of pemetrexed and related analogs have appeared. [46-56]. A practical and scalable synthetic route [56] is depicted in Scheme **9**. Palladium (0) coupling of methyl 4-bromobenzoate (**57**) with 3-butyn-1-ol (**58**) gave crystalline **59**, which was then reduced over palladium on carbon in DCM to give alcohol **60**. Filtration of the catalyst afforded a DCM solution of alcohol **60**, which was utilized directly in a TEMPO-catalyzed sodium hypochlorite oxidation, providing known aldehyde **61** without isolation. Addition of 5,5-dibromobarbituric acid (DBBA) and catalytic amount of HBr in acetic acid to the DCM solution of **61** effected the conversion to α-bromoaldehyde **62**. After aqueous work-up, the solution was concentrated and diluted with acetonitrile to exchange solvents. Addition of commercially available 2,4-diamino-6-hydroxypyrimidine (**63**), aqueous sodium acetate and heating to 45°C resulted in cyclic condensation and precipitation of pyrrolo[2,3-*d*]pyrimidine **64** from the reaction mixture in 67% yield based on **60**. Saponification of **64** with aqueous sodium hydroxide followed by acidification afforded the carboxylic acid derivative **65**, which was elaborated to **66** by chlorodimethoxytriazine active ester coupling method. Reaction of **65** with 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) in the presence of *N*-methylmorpholine in DMF solution followed by reaction of the resulting dimethoxy-*s*-



Scheme 9. Synthesis of pemetrexed disodium (**IX**).

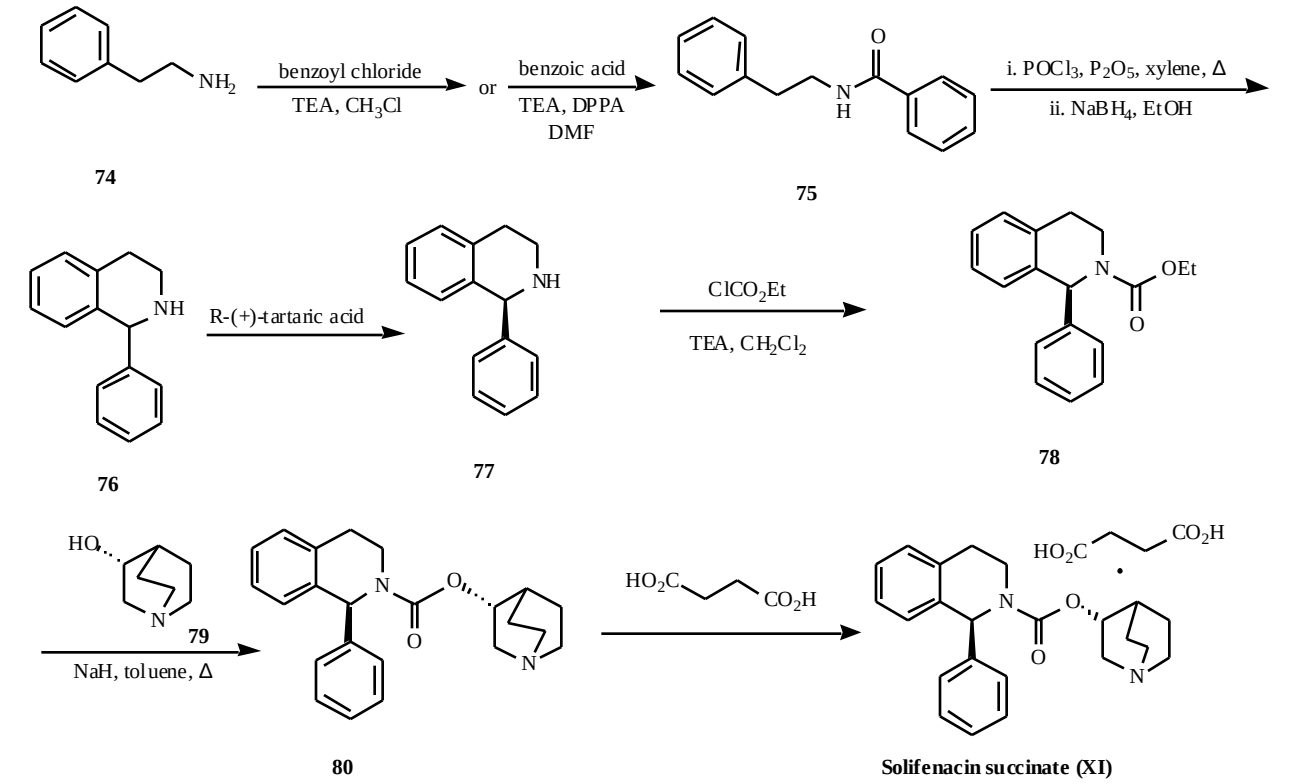


Scheme 10. Synthesis of pregabalin (**X**).

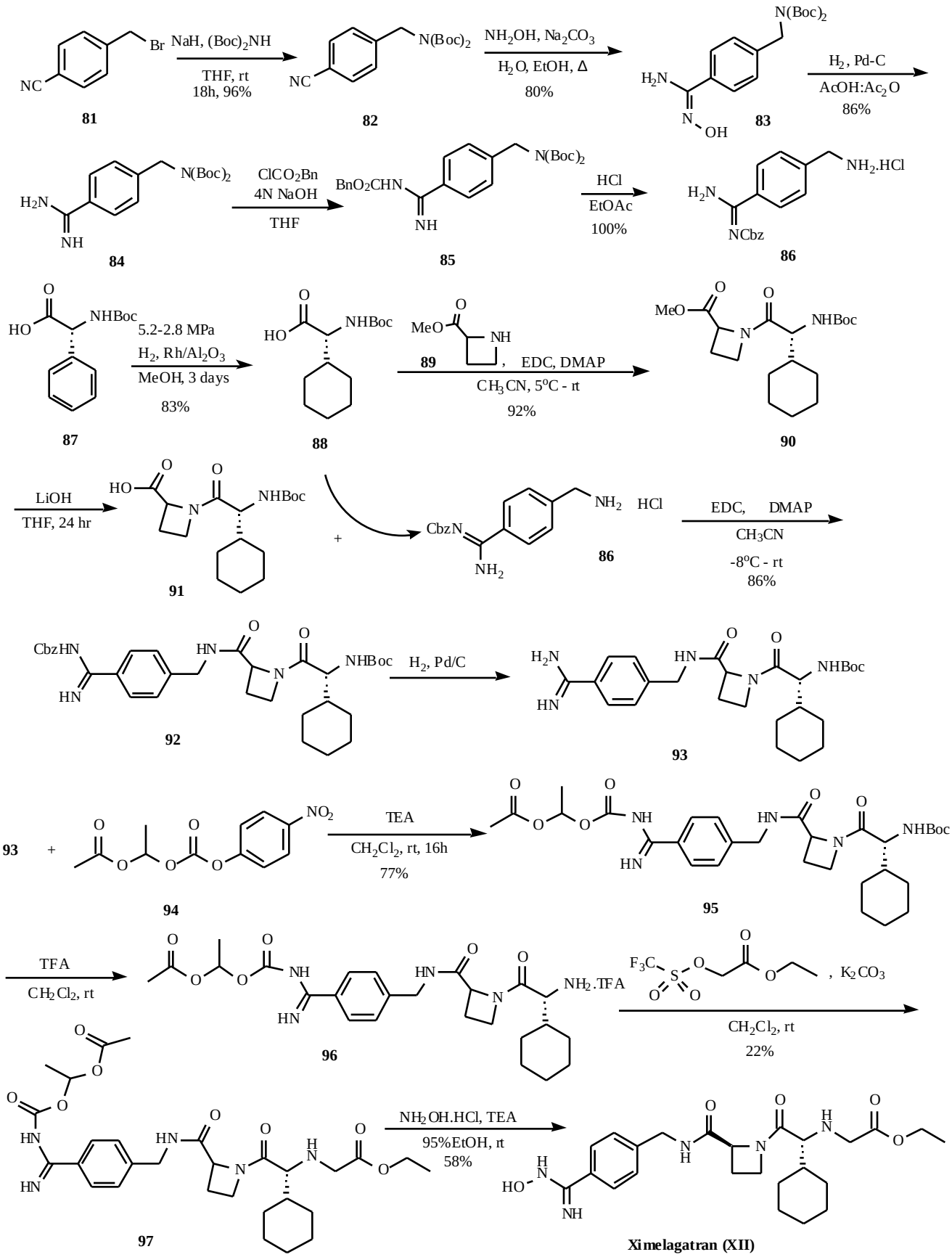
triazinyl ester with diethyl *L*-glutamate afforded crude **66**, which was isolated *via* crystallization as pTSA salt **67**. Saponification of **67** with aqueous sodium hydroxide followed by acidification with HCl gave pemetrexed as the free acid, which was crystallized as disodium salt form.

Pregabalin (*Lyrica*©)

Pregabalin, a GABA mimetic that was developed by Pfizer (originally Warner Lambert) for the treatment of epileptic seizures and neuropathic pain, was approved in European Union in the summer of 2004 and subsquently received approvable letter in September, 2004, in the US [4]. Several syntheses of pregabalin (**X**) have been disclosed in the literature, including process scale-up comparison of several different routes [57-58]. The most cost efficient route as described in the publication [56] is shown in Scheme **10**. Condensation of diethyl malonate **69** in the presense of diisopropyl amine in acetic acid gave α,β-unsaturated diester **70** in high yield. Reaction of the enone diester with potassium cyanide gave cyano diester **71** in 95% yield. In a remarkable three step, one pot process, the nitrile in **71** was hydrolyzed followed by decarboxylation of one of the esters to provide **72** in 73% yield. Resolution of the two enantiomers was achieved using (*S*)-(+)-mandellic acid, one of the best acid found after many salt screening, to give, after two recrystallization, a 99:1 ratio of the desired diastereomer.



Scheme 11. Synthesis of solifenacin succinate (**XI**).



Scheme 12. Synthesis of xilomelagatran (**XII**).

Removal of the acid was done with wet THF instead of base separation, to avoid salt impurities, and one recrystallization in ethanol gave 100% ee diastereomer in 25 – 29% overall yield.

It's worth noting that the Pfizer group have come up with a new process of preparing pregabalin (**X**) *via* enantioselective reduction, that promises to further reduce cost and waste associated with the manufacture of this drug [59-60].

Solfenacin Succinate (*Vesicare*®)

Solifenacin , an orally active selective M_3 muscarinic receptor antagonist, was developed and launched by Yamanouchi for the treatment of overactive bladder (OAB) with symptoms of urgency, frequency and urge incontinence [61]. Solifenacin improves various incontinence associated with OAB by blocking muscarinic receptors on bladder smooth muscles [62]. The synthesis of solifenacin [63] is highlighted in Scheme **11**. Phenylethyl amine (**74**) was reacted with benzoyl chloride or coupled with benzoic acid to give corresponding amide **75**. Reaction with $POCl_3$ and P_2O_5 in refluxing xylene followed by reduction with sodium borohydride in ethanol gave cyclized racemic tetrahydroisoquinoline **76**. The racemic **76** was resolved with (*R*)-(+)-tartaric acid to give 1-(*S*)-phenyl-1,2,3,4-tetrahydroisoquinoline (**77**), which was reacted with ethyl chloroformate and TEA in dichloromethane to give ethyl ester **78**. Compound **78** was transesterified with quinuclidine-3-(*R*)-ol (**79**) with NaH in refluxing toluene to give solifenacin free base as a yellow oil which was treated with succinic acid and re-crystallized to yield solifenacin succinate (**XI**).

Ximelagatran (*Exanta*®)

Ximelagatran (**XII**), a prodrug of a direct thrombin inhibitor, melagatrin, was approved in the European Union in December, 2003, for the prevention of venous thromboembolic events in patients undergoing major elective orthopedic surgery, that is, hip or knee replacement [4-64]. The FDA, however, did not approve the drug in the US based on the recommendation of the advisory panel. Synthesis of melagatran and ximelagatran has been published in several patents and is shown in Scheme **12** [65-68]. The synthesis is based on coupling of key fragment **86** with acid **91** followed by elaboration to provide ximelagatran. The synthesis of the key intermediate, shown in Scheme **12**, was reported to be scalable in high yields [66]. Reaction of benzyl bromide **81** with ditertbutylimino dicarboxylate in the presence of sodium hydride gave **82**, which was reacted with hydroxyl amine in aqueous ethanol to give hydroxyl amidine **83** in 80% yield. Immediate hydrogenation removed the hydroxyl group and gave **84**, which was protected with benzyl chloroformate to provide **85**. Deprotection of **85** with acid furnished amidine intermediate **86**. Synthesis of fragment **91** was done by hydrogenation of *N*-BOC phenyl glycine (**87**) in the presence of rhodium in alumina to provide cyclohexyl amino acid **88** in 83% yield. Coupling of the acid **88** with azetidine 2-methyl ester (**89**) using EDC provided **90** in 92% yield. Hydrolysis of the ester followed by coupling to a key intermediate benzyl carbamate protected aminino benzyl amine **86** under EDC coupling conditions provided **92** in 86%. Subsequent hydrogenolysis removed the benzyl carbamate and provided intermediate **93**. To complete the synthesis, the intermediate **93** was reacted with activated double ester **94** to furnish simultaneously protected and activated amidine **95**. Removal of the BOC group (TFA) followed by reaction with ethyl (*O*-trifluoromethanesulfonyl)-glycolate in the presence of base provided esterified intermediate **97**. Reaction of **97** with hydroxyl amine hydrochloride in the presence of base deprotected and installed hydroxyl amidine product, ximelagatrin (**XII**).

ACKNOWLEDGEMENT

The authors would like to acknowledge the critical evaluation of this review by Robert Chambers.

ABBREVIATIONS

ADME	=	Absorption, distribution, metabolism, excretion
Cbz	=	Carbobenzyloxy
CDMT	=	2-chloro-4,6-dimethoxy-1,3,5-triazine
DBBA	=	5,5-dibromobarbituric acid
DCE	=	Dichloroethane
DCM	=	Dichloromethane
$(DHQD)_2$-PHAL	=	1,4-Bis(9-O-dihydroquininyl)-phthalazine
DIBAL-H	=	Diisobutylaluminum hydride
DIPEA	=	Diisopropylethylamine
DIPP	=	Diisopropylphosphoryl
DMAP	=	4-Dimethylaminopyridine
DMA	=	*N, N*-Dimethylacetamide
DMF	=	*N,N*-Dimethylformamide
DMSO	=	Methyl sulfoxide
DPPA	=	Diphenylphosphoryl azide
MsCl	=	Methansulfonyl chloride
NCE	=	New chemical entities
NMM	=	4-Methylmorpholine
TEA	=	Triethyl amine
TFA	=	Trifluoroacetic acid
THF	=	Tetrahydrofuran
TEMPO	=	2,2,6,6-tetramethyl-1-piperidinyloxy
p-TSA	=	*para*-Toluene sulfonic acid

REFERENCES

[1] Raju, T. N. K. *Lancet* **2000**, *355*, 1022.
[2] Li, J.; Liu, K.-C. *Mini-Rev. Med. Chem.* **2004**, *4*, 207.
[3] Liu, K.-C.; Li, J.; Sakya, S. *Mini-Rev. Med. Chem.* **2004**, *4*, 1105.
[4] Graul, A. I.; Prous, J. R. *Drug News Perspect.* **2005**, *18*, 21.

[5] Issa, J.-P. J.; Kantarjian, H. M.; Kirkpatrick, P. *Nat. Rev.* **2005**, *4*, 275.
[6] Beisler, J. A. *J. Med. Chem.* **1978**, *21*, 204.
[7] Sorm, F.; Piskala, A.; Czechoslovakia, P. *US3350388* **1963**.
[8] Piskala, A.; Sorm, F. *Ger.1922702* **1969**.
[9] Winkley, M. W.; Robins, R. K. *J. Org. Chem.* **1970**, *35*, 491.
[10] Piskala, A.; Sorm, F. *Nucl. Acid Chem.* **1978**, *1*, 435.
[11] Vorbrüggen, H.; Niedballa, U. *Ger.2012888* **1971**.
[12] Niedballa, U.; Vorbrüggen, H. *J. Org. Chem.* **1974**, *39*, 3672.
[13] Ionescu, D.; Blumbergs, P. *US0186283 A1* **2004**.
[14] Ahn, S. K.; Choi, N. S.; Jeong, B. S.; Kim, K. K.; Journ, D. J.; Kim, J. K.; Lee, S. J.; Kim, J. W.; Hong, C. I.; Jew, S. S. *J. Heterocyclic Chem.* **2000**, *37*, 1141.
[15] Hong, C. I.; Kim, J. W.; Lee, S. J.; Ahn, S. K.; Choi, N. S.; Kim, K. K.; Jeong, B. S. *WO9902530* **1999**.
[16] Henk, H. *Chem. Ber.* **1949**, *82*, 36.
[17] Wani, M. c.; Ronman, P. E.; Lindley, J. T.; Wall, M. E. *J. Med. Chem.* **1980**, *23*, 554.
[18] Terasawa, H.; Sugimor, M.; Ejima, A.; Tagawa, H. *Chem. Pharm. Bull.* **1989**, *37*, 3382.
[19] Jew, S. S.; Ok, K. D.; Kim, H. J.; Kim, M. G.; Kim, J. M.; Hah, J. M.; Cho, Y. S. *Tetrahedron Asymmetry* **1995**, *6*, 1248.
[20] Kingsbury, W. D.; Boehm, J. C.; Jakas, D. R.; Holden, K. G.; Hecht, S. M.; Gallagher, G.; Caranfa, M. J.; McCabe, F. L.; Faucette, L. F.; Johnson, R. K.; Hertzberg, R. P. *J. Med. Chem.* **1991**, *34*, 98.
[21] Balfour, J. A. B.; Scott, L. J. *Drugs* **2005**, *65*, 271.
[22] Linberg, J. S.; Moe, S. M.; Goodman, W. G.; Sprague, S. M.; Liu, W.; Blaisdell, P. W.; Brenner, R. M.; Turner, S. A.; Martin, K. J. *Kidney Int.* **2003**, *63*, 248.
[23] Van Wagenen, B. C.; Moe, S. M.; Balandrin, M. F.; Delmar, E. G.; Nemeth, E. F. *US6211244* **2001**.
[24] Kirwin, J. L.; Goren, J. L. *Pharmacotherapy* **2005**, *25*, 396.
[25] McCormack, P. L.; Keating, G. M. *Drugs* **2004**, *64*, 2567.
[26] Bymaster, F. P.; Beedle, E. E.; Findlay, J.; Gallagher, P. T.; Krushinski, J. H.; Mitchell, S.; Robertson, D. W.; Thompson, D. C.; Wallace, L.; Wong, D. T. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4477.
[27] Frampton, J. E.; Easthope, S. E. *Drugs* **2004**, *64*, 2475.
[28] Hidalgo, M.; Bloedow, D. *Semin. Oncol.* **2003**, *30*, 25.
[29] *Drugs R&D* **2003**, *4*, 243.
[30] Schnur, R. C.; Arnold, L. D. *WO 9630347A1* **1996**.
[31] Schnur, R. C.; Arnold, L. D. *US5747498* **1998**.
[32] Lehner, R. S.; Norris, T.; Santafianos, D. P. *EP1044969* **2000**.
[33] Vogal, T. J.; Kummel, S.; Hammerstingl, R.; Schellenbeck, M.; Schumacher, G.; Balzer, T.; Schwarz, W.; Müller, P. K.; Bechstein, W. O.; Mack, M. G.; Söllner, O.; Felix, R. *Radiology* **1996**, *200*, 59.
[34] Schuhmann-Giampieri, G.; Schmitt-Willich, H.; Press, W. R.; Negishi, C.; Weinmann, H. J.; Speck, U. *Radiology* **1992**, *183*, 59.
[35] Vander Elst, L.; Maton, F.; Laurent, S.; Seghi, F.; Chapelle, F.; Muller, R. N. *Magn. Reson. Med.* **1997**, *38*, 604.
[36] Schmitt-Willich, H.; Brehm, M.; Ewers, C. L. J.; Michl, G.; Müller-Fahrnow, A.; Petrov, O.; Platzek, J.; Radüchel, B.; Sülzle, D. *Inorg. Chem.* **1999**, *38*, 1134.
[37] Fujiwara, T. *Jap. Pharma. Therap.* **2005**, *33*, 17.
[38] Rabasseda, X.; Mealy, N.; Castaner, J. *Drugs Future* **1995**, *20*, 780.
[39] Kikuchi, H.; Satoh, H.; Yahata, N.; Hagihara, K.; Hayakawa, T.; Mino, S.; Yanai, M. *EP0469449* **1992**.
[40] Yamaguchi, T.; Yanagi, T.; Hokari, H.; Mukaiyama, Y.; Kumijo, T.; Yamamoto, I. *Chem. Pharm. Bull.* **1998**, *46*, 337.
[41] Yamaguchi, T.; Yanagi, T.; Hokari, H.; Mukaiyama, Y.; Kamijo, T.; Yamamoto, I. *Yakugaku Zasshi* **1998**, *118*, 248.
[42] Sato, F.; Tsubaki, N.-K.; Hokari, H.; Tanaka, N.; Saito, M.; Akahane, K.; Kobayashi, M. *EP0507534A1* **1992**.
[43] Sato, J.; Hayashibara, T.; Torihara, M.; Tamai, Y. *WO2002085833 A1* **2002**.
[44] Kamijo, T.; Yamaguchi, T.; Yanagi, T. *WO9832736 A1* **1998**.
[45] Liu, J.; Yang, Y.; Ji, R. *Helv. Chim. Acta* **2004**, *87*, 1935.
[46] Schönfeld, F.; Troschütz, R. *Heterocycles* **2001**, *55*, 1679.
[47] Taylor, E. C.; Patel, H. H.; Sabitha, G.; Chaudhari, R. *Heterocycles* **1995**, *43*, 349.
[48] Barnett, C. J.; Wilson, T. M. *Heterocycles* **1993**, *35*, 925.
[49] Shih, C.; Grossett, L. S. *Heterocycles* **1993**, *35*, 825.
[50] Taylor, E. C.; Patel, H. H. *Tetrahedron* **1992**, *48*, 8089.
[51] Miwa, T.; Hitaka, T.; Akimoto, H. *J. Org. Chem.* **1993**, *58*, 1696.
[52] Taylor, E. C.; Young, W. B. *J. Org. Chem.* **1995**, *60*, 7947.
[53] Taylor, E. C.; Liu, B. *WO0011004* **2000**.
[54] Taylor, E. C.; Liu, B. *J. Org. Chem.* **2003**, *68*, 9938.
[55] Barnett, C. J.; Wilson, T. M. *US5416211* **1995**.
[56] Barnett, C. J.; Wilson, T. M.; Kobierski, M. E. *Org. Process Res. Dev.* **1999**, *3*, 184.
[57] Yuen, P.-W.; Kanter, G. D.; Taylor, C. P.; G., V. M. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 823.
[58] Hoekstra, M. S.; Sobieray, D. M.; Schwindt, M. A.; Mulhern, T. A.; Grote, T. M.; Huckabee, B. K.; Hendrickson, V. S.; Franklin, L. C.; J., G. E.; Karrick, G. L. *Org. Proc. Res. Dev.* **1997**, *1*, 26.
[59] Burk, M. J.; de Koning, P. D.; Grote, T. M.; Hoekstra, M. S.; Hoge, G.; Jennings, R. A.; Kissel, W. S.; Le, T. V.; Lennon, I. C.; Mulhern, T. A.; Ramsden, J. A.; Wade, R. A. *J. Org. Chem.* **2003**, *68*, 5731.
[60] Burk, M. J.; Goel, O. P.; Hoekstra, M. S.; Mich, T. F.; Mulhern, T. A.; Ramsden, J. A. *WO 0155090 A1* **2001**.
[61] Robinson, D.; Cardozo, L. *Exp. Opin. Invest. Drugs* **2004**, *13*, 1339.
[62] Chilman-Blair, K.; Bosch, J. L. H. R. *Drugs Today* **2004**, *40*, 343.
[63] Takeuchi, M.; Naito, R.; Hayakawa, M.; Okamoto, Y.; Yonetoku, Y.; Ikeda, K.; Isomura, Y. *EP0801067* **1996**.
[64] Sorbera, L. A.; Castaner, J.; Silvestre, J. S.; Bayes, M. *Drugs Future* **2001**, *26*, 1155.
[65] Lila, C.; Gloanec, P.; Cadet, L.; Herve, Y.; Fournier, J.; Leborgne, F.; Verbeuren, T. J.; De Nanteuil, G. *Synth. Commun.* **1998**, *28*, 4419.
[66] Eriksson, B. I.; Carlsson, S.; Halvarsson, M.; Risberg, B.; 1. Antonsson, K. T.; Bylund, R. E.; Gustafsson, N. D. *WO9429336A1* **1994**.
[67] Hedström, L.; Lundblad, A.; Nagard, S. *WO0102426A1* **2001**.
[68] Antonsson, K. T.; Gustafsson, D.; Hoffman, K.-J.; Nyström, J.-E.; Sörensen, H.; Sellén, M. *WO9723499A1* **1997**.