Heterocyclic Templates and Nonpolyglutamatable Inhibitors of Thymidylate Synthase as Potential Antitumour Agents: A Chemical Perspective

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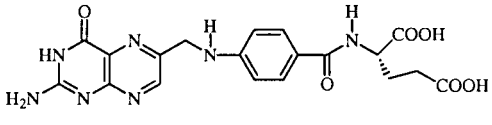
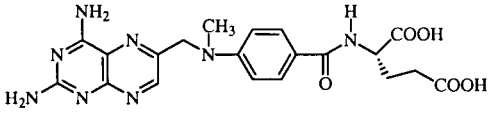
Antifolates form a major part of antimetabolites as anticancer agents, in particular since the discovery in 1948 of methotrexate, a structural analogue of folic acid [1].



Folic acid



Methotrexate

In fact, methotrexate is still in clinical use for the treatment of a wide range of tumours, both as a single agent and in combination chemotherapy [2]. It is believed that methotrexate exerts its antitumour activity by inhibiting the enzyme dihydrofolate reductase [3] which catalyses the reduction of 7,8-dihydrofolic acid to 5,6,7,8-tetrahydrofolic acid thus preventing the recycling of 7,8-dihydrofolic acid to 5,6,7,8-tetrahydrofolic acid (Figure 1). As a result, the synthesis of thymidylate is blocked since N^5,N^{10}-methylenetetrahydrofolate, a cofactor required for thymidylate synthesis, is directly derived from 5,6,7,8-tetrahydrofolic acid. Furthermore, inhibition of dihydrofolate reductase by methotrexate blocks purine nucleotide biosynthesis since 5,6,7,8-tetrahydrofolic acid is a precursor for 10-formyl-5,6,7,8-tetrahydrofolic acid which is

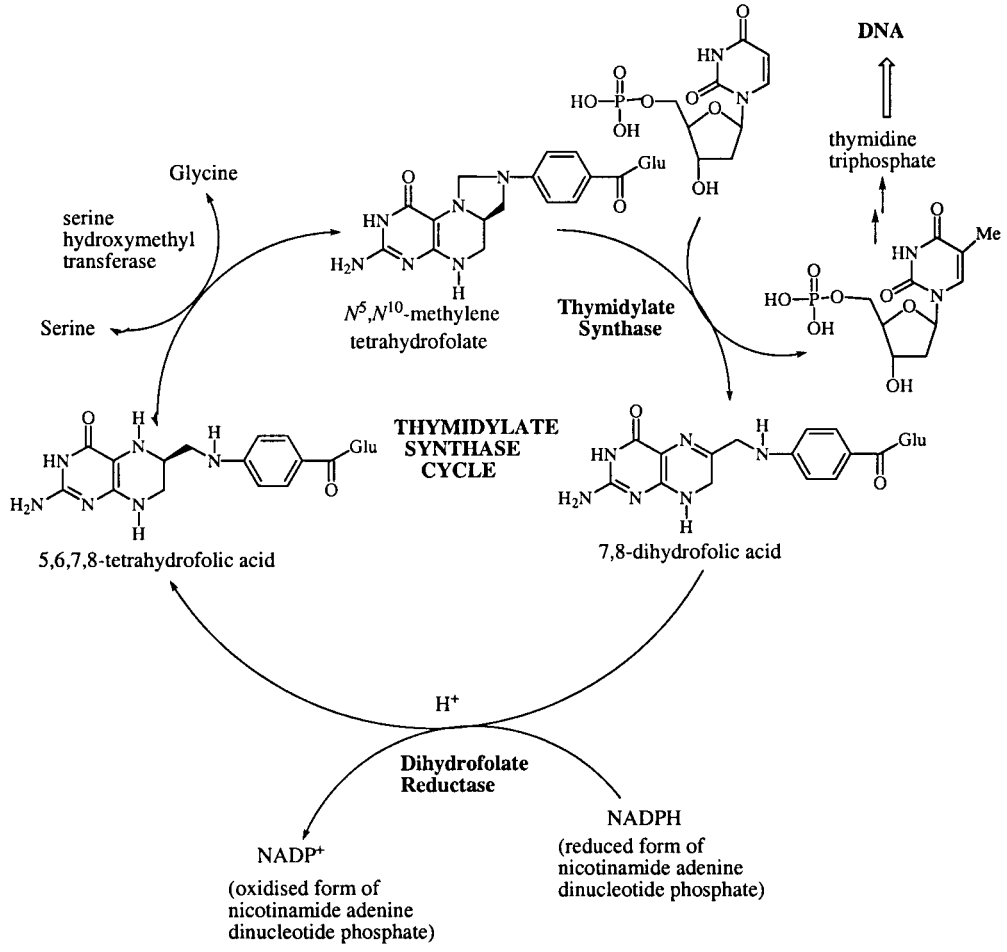
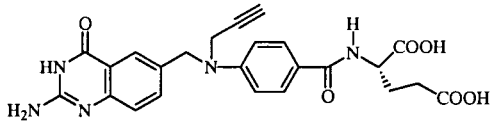


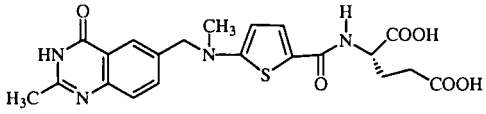
Figure 1. Thymidylate Synthase Cycle

involved in the *de novo* pathway of purine biosynthesis [4].

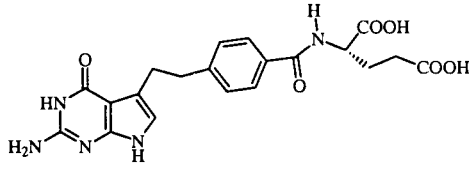
A second approach to the development of antifolates is to target the thymidylate synthase enzyme rather than dihydrofolate reductase. Thymidylate synthase catalyses the *de novo* synthesis of thymidylate, exlusively required in DNA synthesis (Figure **1**). Its inhibition is expected not to interfere with purine biosynthesis in contrast to dihydrofolate reductase, therefore, an inhibitor of thymidylate synthase may display a better therapeutic index than methotrexate. The prototype folate-based inhibitor of thymidylate synthase is considered to be CB 3717, a compound which was first synthesised at the Institute of Cancer Research, UK [5-7]. Although the clinical usefulness of this compound was limited because of its dose-limiting renal toxicity, its antitumour activity prompted many research groups to intensify their search for a clinically suitable inhibitor of thymidylate synthase. As a result, raltitrexed, developed jointly by the Institute of Cancer Research and Zeneca Pharmaceuticals, is now widely registered for the treatment of colorectal cancer [8-11].



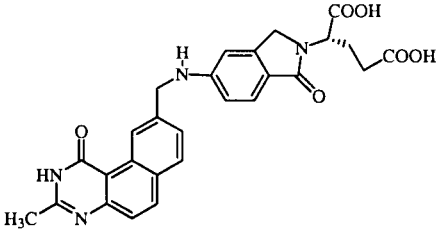
CB3717



raltitrexed



LY231514



BW1843U89

Other polyglutamatable inhibitors of thymidylate synthase have also reached the stage of clinical evaluation. They include BW1843U89, a benzo[*f*]quinazoline-based inhibitor [12-14], and LY231514, a pyrrolo[2,3-*d*]pyrimidine-based inhibitor, although the latter is now believed to be a multitargeted antifolate [15-16]. It should be noted that generally the polyglutamate forms are more cytotoxic than their monoglutamate precursors, so in this respect polyglutamation could be considered as a desirable metabolic process. However, in the last decade much research in the antifolate area was directed towards the development of nonpolyglutamatable inhibitors of thymidylate synthase. The main reason for this was to overcome resistance to synthetic antifolates, due to low level of, or an altered folylpolyglutamyl synthetase [17, 18] or to increased activity of γ-glutamyl hydrolases [19] a group of enzymes that catalyses the hydrolysis of the γ-glutamyl amide bond of polyglutamates.

The molecules synthesised for this purpose are based on a number of heterocyclic templates which could be categorized as follows: 1) quinazolin-4(3*H*)-ones, 2) benzo[*f*]quinazolin-1(2*H*)-ones, 3) 6,7-imidazotetrahydroquinolines, 4) benzo[*cd*]indoles, and 5) pyrrolo[2,3-*d*]-pyrimidines. These heterocyclic templates were introduced either as a result of a classical medicinal chemistry approach or by using rational drug design. In some cases their synthesis was accomplished by developing novel chemistry. Since the structural activity relationship for the nonpolyglutamatable inhibitors of thymidylate synthase has been recently reviewed [20], we will attempt, in this article, to review the synthetic pathways to the heterocyclic templates. We will also attempt to highlight the main synthetic strategies employed for the preparation of the final antifolates.

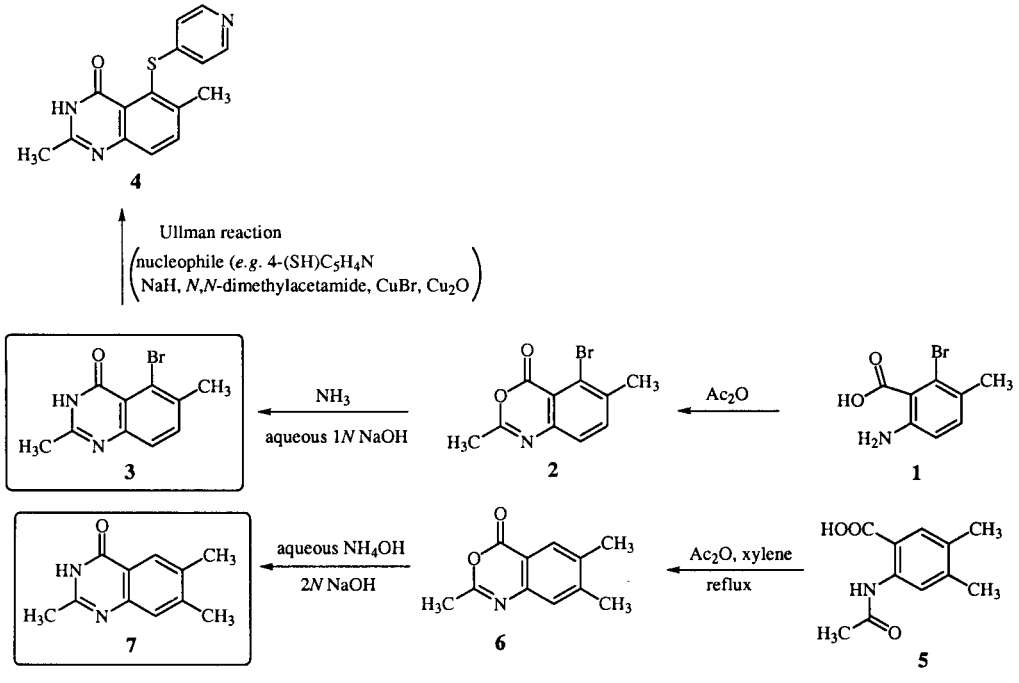
1. Quinazolin-4(3*H*)-one-based Molecules.

1.1 2-Methylquinazolin-4(3*H*)-ones.

Since CB 3717, the prototype inhibitor of thymidylate synthase, is a quinazolin-4(3*H*)-one-based molecule, there is no surprise that the majority of inhibitors of thymidylate synthase are based on this structural template.

The majority of synthetic routes to 2-methylquinazolin-4-(3*H*)-ones are based on the Niementowski reaction that proceeds *via* an *o*-amidobenzamide intermediate [21]. In recent years, 2-methylquinazolin-4(3*H*)-ones were most effectively synthesised from their respective anthranilic acid derivatives *via* a benzoxazinone intermediate (Scheme 1). For example, Webber *et al.* utilised this methodology to synthesise 5-bromo-2,6-dimethylquinazolin-4(3*H*)-one (**3**) [22]. First, the anthranilic acid derivative **1** was converted into the benzoxazinone **2** upon treatment with acetic anhydride (Scheme 1). Subsequent treatment of **2** with anhydrous ammonia and then aqueous 1*N* sodium hydroxide gave the desired product **3**. 5-Bromo-6-methoxy-2-methylquinazolin-4(3*H*)-one, 5-bromo-6-ethyl-2-methylquinazolin-4(3*H*)-one, and 5-chloro-2-methylquinazolin-4(3*H*)-one were also prepared in a

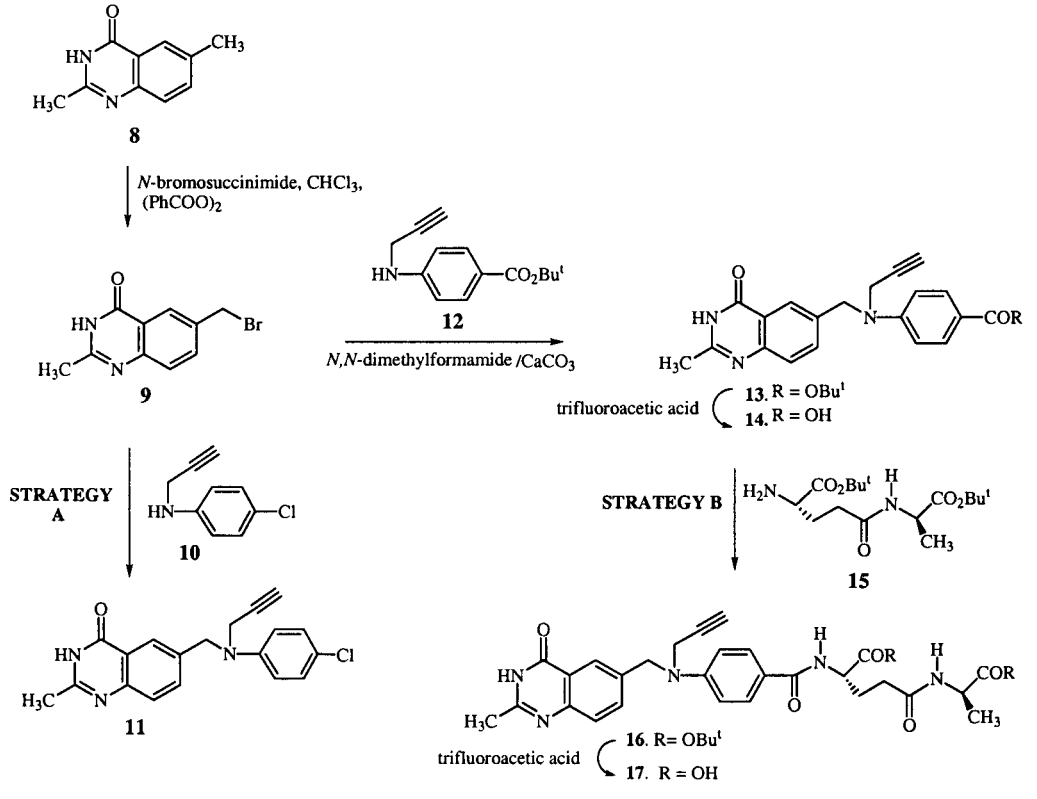
Scheme 1



similar manner by the same group. Utilization of the Ullman reaction then afforded a series of 5-(arylthio)-quinazolin-4(3*H*)-ones such as **4** (Scheme 1), a novel class of lipophilic inhibitors of thymidylate synthase.

The quinazolin-4(3*H*)one **7** (Scheme 1) was prepared by Marsham *et al.* in a similar fashion [23]. 6-Methylquinazolin-4(3*H*)-ones such as **7** and **8** were the key intermediates for the preparation of a variety of

Scheme 2



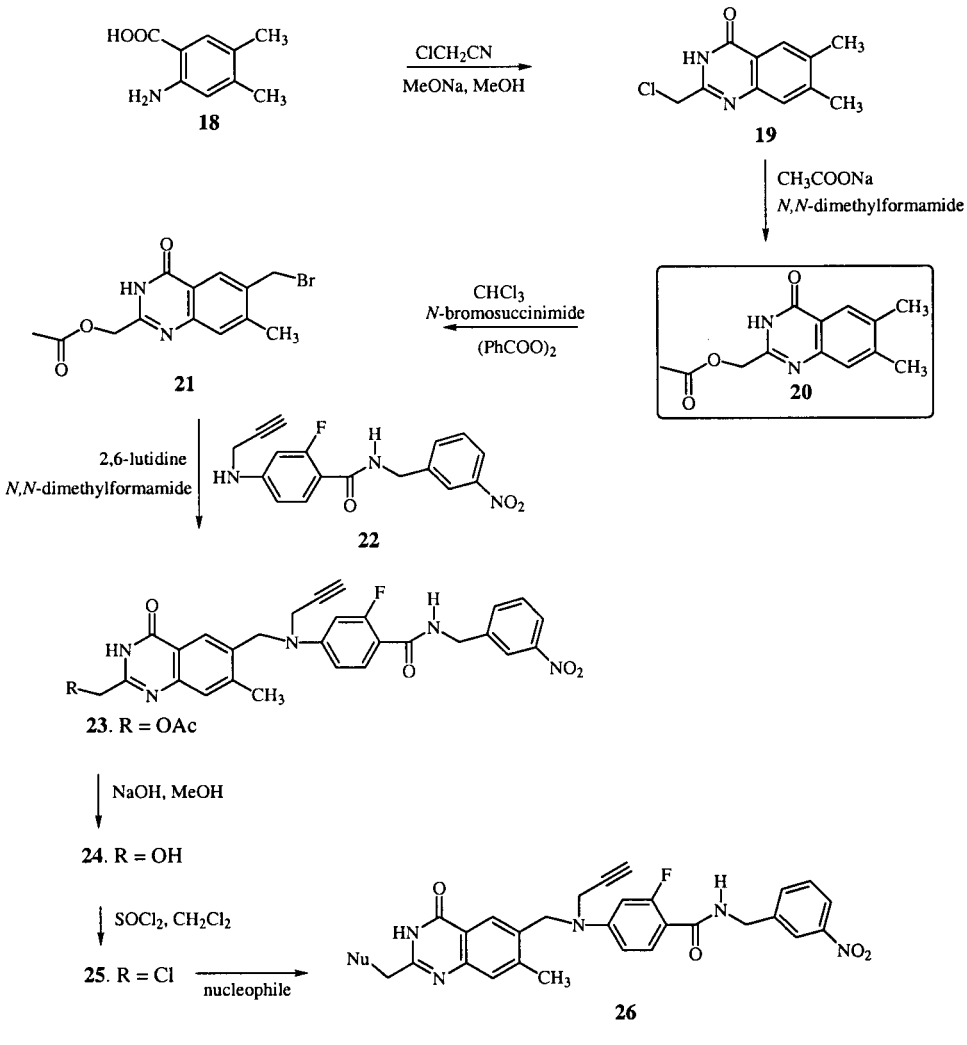
6-substituted quinazolin-4(3*H*)-one-based inhibitors of thymidylate synthase. As it can be seen in Scheme 2, two strategies were employed for the synthesis of the final products. In the first strategy, more often utilised to prepare lipophilic inhibitors of thymidylate synthase, a 6-bromomethylquinazolin-4(3*H*)-one derivative is coupled to the appropriate aniline derivative to afford the final product. For example, the lipophilic inhibitor of thymidylate synthase **11** was prepared by Jones *et al.* by coupling of 6-bromomethyl-2-methylquinazolin-4(3*H*)-one (**9**) to 4-chloro-*N*-prop-2-ynylaniline (**10**) [24]. In the second approach, a pteroic acid analogue is first synthesised. Subsequent coupling to the appropriate ligand followed by the removal of the protecting groups, if necessary, affords the final antifolates. For example, a series of dipeptide-containing inhibitors of thymidylate synthase, such as the dipeptide derivative **17**, was prepared by Bavetsias *et al.* employing this strategy [25-26].

1.2 2-Hydroxymethylquinazolin-4(3*H*)-ones.

General synthetic methodologies to 2-hydroxymethylquinazolin-4(3*H*)-ones are limited, though 2-hydroxymethylquinazolin-4(3*H*)-one has been prepared by three different routes: cyclisation of 2-acetoxyacetamidobenzamide under alkaline conditions [27], fusion of anthranilamide with ethyl glycolate [28], reacting 4,1-benzoxazepine-2,5(1*H*,3*H*)-dione with ammonia in methanol [29]. The most effective route to 2-hydroxymethylquinazolin-4(3*H*)-ones was developed by Hennequin *et al.* for the synthesis of lipophilic inhibitors of thymidylate synthase with modification to the C2-methyl substituent [30] (Scheme 3).

The key step in this route involves converting anthranilic acid derivatives such as **18** into the corresponding 2-chloromethylquinazolin-4(3*H*)-ones using chloroacetonitrile in methanol in the presence of catalytic amounts of sodium methoxide (Scheme 3). Subsequent nucleophilic substitution of the chloride by the acetate anion affords 2-acetoxymethylquinazolin-4(3*H*)-ones (*i.e.*

Scheme 3



2-hydroxymethylquinazolin-4(3*H*)-ones where the hydroxyl functionality is protected as an acetate ester).

Further modifications at the 2-position were effected at the last steps of the synthesis (Scheme 3). For example, alkaline hydrolysis of the acetate ester of **23** followed by treatment of the resulting alcohol with thionyl chloride afforded the 2-chloromethylquinazolin-4(3*H*)-one-based antifolate **25**. Displacement of the chloride with nucleophiles (amines, thiolate anions) gave a range of quinazolin-4(3*H*)-one-based inhibitors of thymidylate synthase bearing a variety of C-2 methyl substituents.

1.3 2-Aminoquinazolin-4(3*H*)-ones.

In some early reports 2-aminoquinazolin-4(3*H*)-ones were prepared from the corresponding 2,4-diaminoquinazolines by hydrolysis under strong acidic conditions [31,32]. The most commonly used methodology to 2-aminoquinazolin-4(3*H*)-ones involves the cyclisation of methyl or ethyl esters of anthranilic acids with guanidine [33] (Scheme 4). Indeed, McNamara *et al.* synthesised 2-amino-6-methylquinazolin-4(3*H*)-one (**28**) from ethyl 2-amino-5-methyl benzoate (**27**) on treatment with guanidine in ~80% yield [34]. Interestingly, the same transformation was achieved in a higher yield (99%) by simply using the rather forgotten chloroformamidine hydrochloride instead of guanidine [34]. Similarily, Webber *et al.* employed chloroanthranilic acids *via* the isatoic anhydrides **30** which were formed on treatment with bis(trichloromethyl)carbonate. Subsequent ring opening to the methyl esters **31a,b** was accomplished quantitatively with refluxing dry methanol.

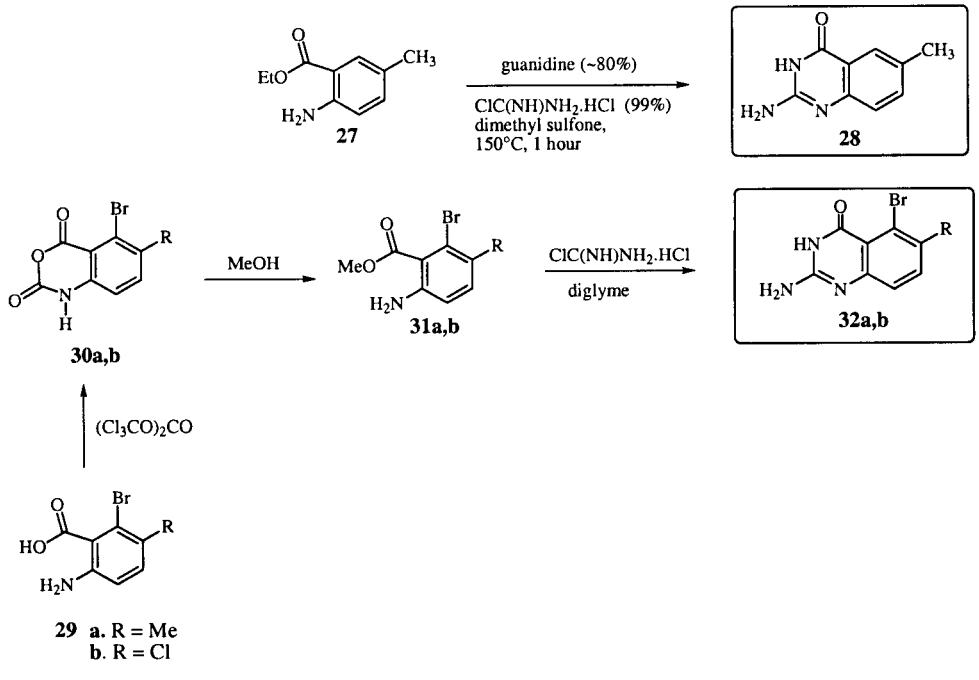
2. Benzo[*f*]quinazolin-1(2*H*)-ones.

The general route to 5,6-dihydrobenzo[*f*]quinazolin-1(2*H*)-ones **34a** and **34b** involved the cyclisation of ethyl or methyl 3,4-dihydro-2-hydroxy-1-naphthoate with guanidine or acetamidine respectively (Scheme 5) [35]. The full aromatic systems, benzo[*f*]quinazolin-1(2*H*)-ones **35a,b** were obtained from **34a,b** utilising one of the following three methodologies: a) bromination/dehydrobromination with *N*-bromosuccinimide, b) dehydrogenation with palladium/charcoal, and c) upon treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in benzene. For methodologies a and c the amino functionality was protected with the pivaloyl group which was removed after the oxidation with aqueous sodium hydroxide.

3. 6,7-Imidazotetrahydroquinolines.

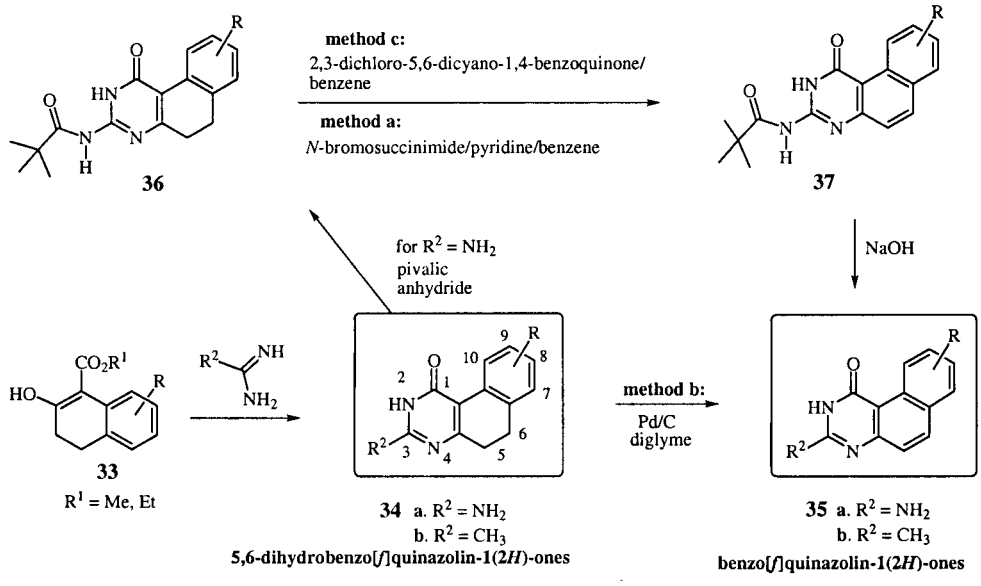
A structure-based design approach led to synthesis of lipophilic inhibitors of thymidylate synthase based on the 6,7-imidazotetrahydroquinoline heterocyclic template [36]. The synthesis here begins with either 6-aminotetrahydroquinoline (**38**) or 6-acetamidoquinoline (**39**)

Scheme 4



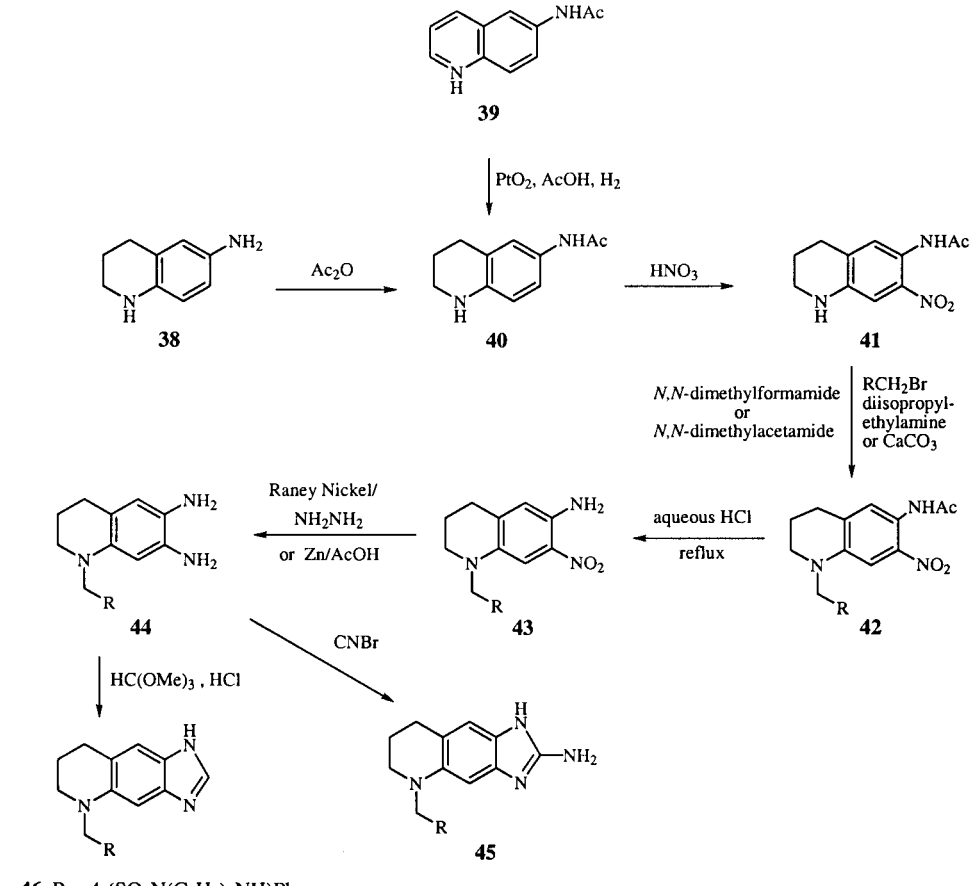
formamidine hydrochloride for the cyclisation of the methyl esters **31a,b** to the corresponding 2-aminoquinazolin-4(3*H*)-ones **32** (Scheme 4) [22]. It should be noted that the methyl esters **31a,b** were prepared from the corresponding (Scheme 6). The former is converted into **40** with acetic anhydride and the latter by catalytic hydrogenation. In the next step, nitration is effected with nitric acid and then **41** is alkylated with a variety of benzylic type bromides. The

Scheme 5



key intermediate to the 6,7-imidazotetrahydroquinoline template was the diamine **44** which was derived from **42** by first removing the acetyl group under acidic conditions and then reducing the nitro group with either Raney Nickel/hydrazine or zinc/acetic acid (Scheme 6). In the final step cyclisation of **44** with cyanogen bromide

Scheme 6



afforded 2-aminoimidazotetrahydroquinolines **45**. On the other hand, the unsubstituted derivative **46** was obtained from **44** (R = 4-($SO_2N(C_2H_4)_2NH$)Ph) on treatment with trimethyl orthoformate-hydrochloric acid.

4. Benz[*cd*]indole Heterocyclic Template.

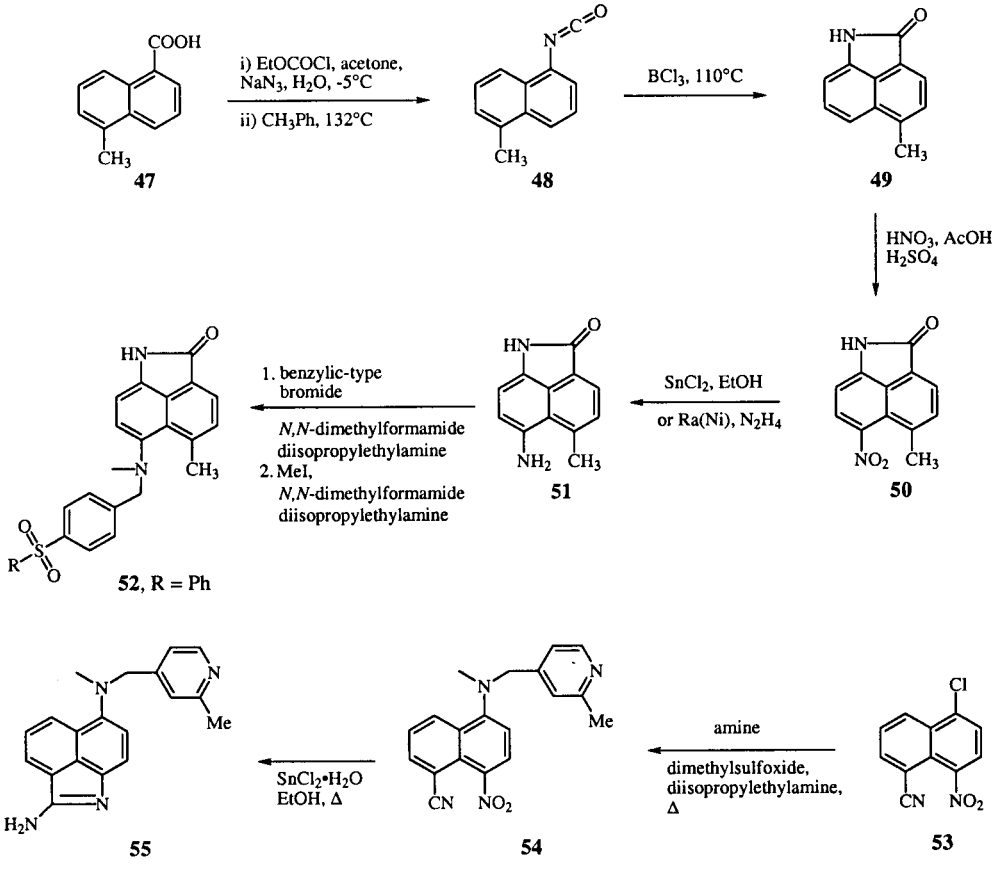
This novel structural template in the antifolate area was introduced by Varney *et al.* on the basis of protein crystal structure analysis [37]. The key intermediates for this class of compounds were 5-chlorobenz[*cd*]indol-2(1*H*)-one and 5-methylbenz[*cd*]indol-2(1*H*)-one (**49**). For 5-methylbenz[*cd*]indol-2(1*H*)-one-based molecules (Scheme 7) the synthesis begins with the acid **47** which is first converted into its respective acyl azide *via* mixed carbonic anhydride carboxyl activation. The azide is then rearranged to the isocyanate **48** on heating in boiling toluene. Cyclisation of **48** to give 5-methylbenz[*cd*]indol-2(1*H*)-one (**49**) was effected at 110° using boron trichloride as a Lewis acid. Nitration of **49** followed by the reduction of the nitro group gave the intermediate **51** which on alkylation with the appropriate electrophiles afforded the final products, such as **52**. For the preparation of 2,6-diaminobenz[*cd*]indole-containing molecules, such as **55**, by Varney *et al.* [38], the synthetic sequence has been reversed since the indole moiety was constructed at the last step (Scheme 7). The presence of a nitro group on the naphthalene nucleus facilitated the nucleophilic aromatic substitution of the chloride at the 4-position of **53** by an appropriate amine. Subsequent reduction of the nitro group with tin(II) chloride on heating in ethanol led to the formation of 2,6-diaminobenz[*cd*]indole-based inhibitors of thymidylate synthase.

5. Pyrrolo[2,3-*d*]pyrimidine-Based Inhibitors of Thymidylate Synthase.

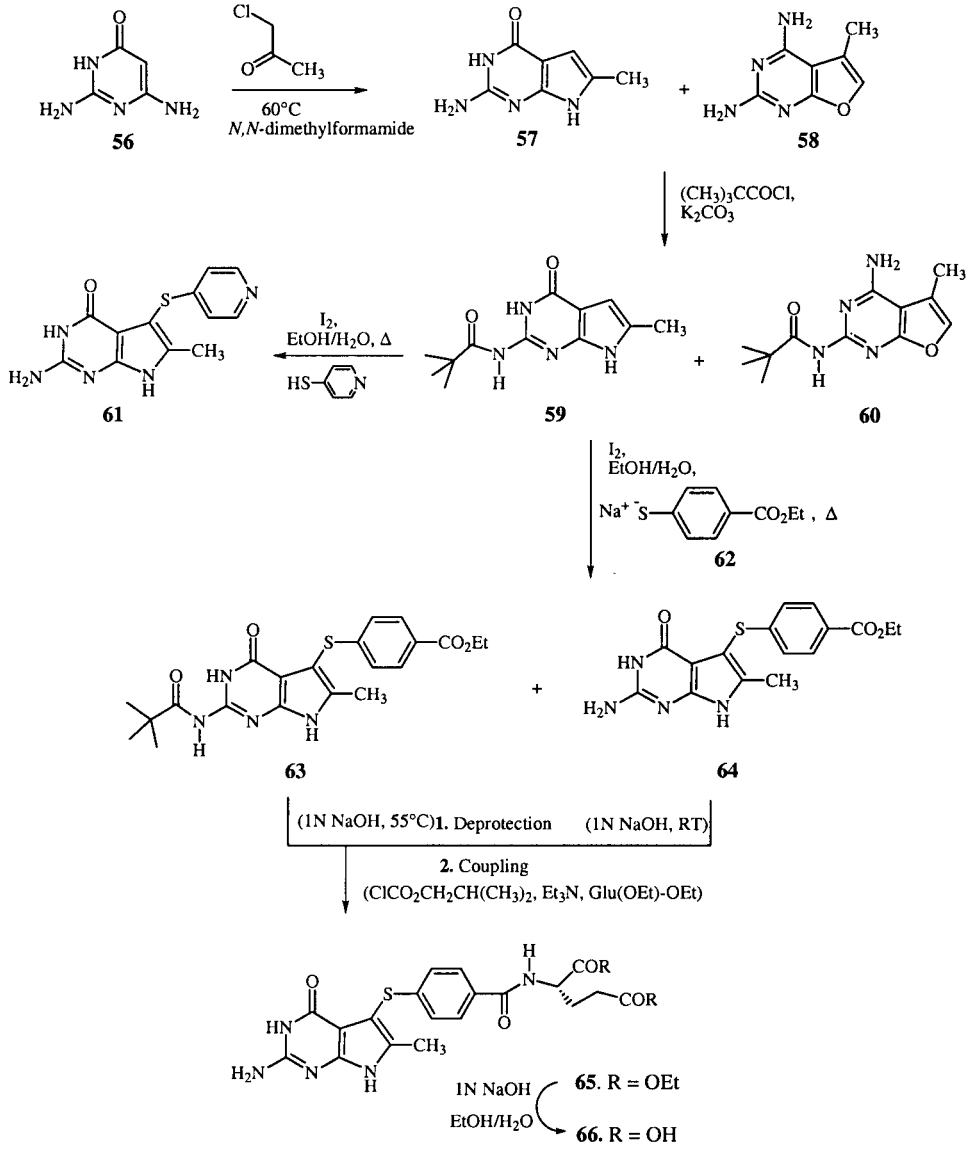
This class of inhibitors of thymidylate synthase is mainly associated with compounds **61** and **66**, reported by Gangjee *et al.* [39].

The route to **61** is outlined in Scheme 8. The pyrrolo[2,3-*d*]pyrimidine ring was first constructed by reacting 2,6-diamino-4-oxopyrimidine (**56**) with chloroacetone. Following pivaloylation of the amino group, the desired product **59** was isolated and then converted into the target compound **61** by treatment with 4-mercaptopyridine in a mixture of ethanol/water with 2 equivalents of iodine at 80° [39]. The same methodology was also utilised to synthesize the glutamate derivative **66** (Scheme 8) [39]. So, treatment of a solution of **59** and iodine with an ethanolic solution of mercaptan **62** gave compounds **63, 64**. Removal of the protecting

Scheme 7



Scheme 8



groups under alkaline conditions was followed by condensation with diethyl glutamate *via* isobutyl chloroformate coupling. Hydrolysis of the ethyl ester with 1*N* sodium hydroxide in ethanol/water afforded the final product **66**.

Acknowledgements.

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