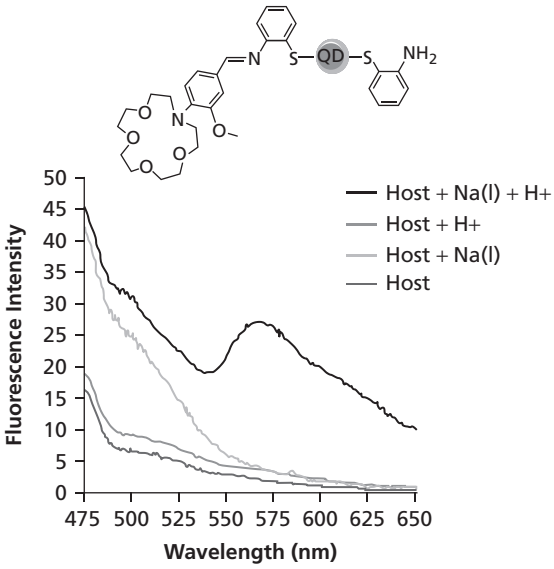

Figure 1 AND logic behaviour of probe.

15-crown-5 receptor. This was then subjected to a Vilsmeir formylation reaction and the resulting aldehyde attached to the QD through a facile Schiff base reaction. The extent of attachment was determined to be 20% by 1H NMR spectroscopy. Therefore, the QD possesses two receptors, the crown ether selective for sodium and the aniline selective for protons. Fluorescence measurements were conducted in aqueous-based samples buffered at 7.0 with HEPES buffer and recorded on a Perkin-Elmer LS55 spectrophotometer.

Results and Discussion

The QD emission of the probe (λ_{MAX} = 560 nm) was quenched in the absence of Na+ or H+ when excited at 370 nm due to photo-induced electron transfer (PET) from the receptors to the excited QD. Upon the simultaneous addition of Na+ (10-3 M) and H+ ions (10-6.2 M), QD fluorescence was recovered due to the PET process being cancelled when the receptors bind their ions (Figure 1). However the independent addition of Na+ or H + resulted in no recovery of QD fluorescence. Thus, the probe functions as a two-input AND molecular logic gate with Na+ and H+ as inputs and λ_{MAX} = 560-nm fluorescence as the output.

Conclusions

A QD-based molecular probe that enables the detection of Na+ and H+ only when both are present over a threshold value has been synthesised. Thus, the conditions of a two-input AND logic gate are satisfied. This is the first example of a QD-based AND molecular logic gate for H+ and Na+ and benefits from the improved photophysical properties QDs offer.

Short Papers in Medicinal Chemistry

10
Design, synthesis and evaluation of iron chelators to identify a prospective prophylactic agent for Alzheimer's disease

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Introduction and Objectives

The contribution of metal ions, especially iron, in mediating neurotoxicity either by favouring beta-amyloid plaque formation or by redox cycling in Alzheimer's disease (AD) brain has already been established.[1] Hence, the selective chelation of beta-amyloid-associated iron is a prospective therapeutic approach for the prophylaxis of AD. Ideally, an iron chelator should be able to cross the blood–brain barrier (BBB) and exhibit neuroprotective efficacy against oxidative stress in AD brain to act prophylactically. The present work aims to identify a lead compound with such properties from a library of bidentate iron chelators.

Method

Several bidentate iron chelators (3-hydroxypyridin-4-ones) were synthesised based on the structure of deferiprone, a chelator used in the treatment of iron-overloaded thalassemia major. Structural considerations to assist BBB permeability were observed in designing these chelators. In-situ brain perfusion was carried out on guinea pigs using these chelators and deferiprone. High-performance liquid chromatography of extracts from guinea pig brains was used to quantify the BBB influx efficiency of each chelator. Chelators with a higher BBB influx efficiency than that of deferiprone have been selected for neuronal cell culture studies in order to evaluate their neuroprotective efficacy against various oxidative insults.

Results and Discussion

Total synthesis of ten 3-hydroxypyridin-4-ones was carried out; their molecular weights varied from 157 to 207, and their log $D_{7.4}$ values fell in the range of −1 to 1. All animal experiments were performed in accordance with the Animals (Scientific Procedures) Act 1986. A steady state of in-situ brain perfusion was determined at a flow rate of 6 ml/min of brain perfusate for 15–20 min with an 800 μM chelator concentration. The BBB influx efficiency of the chelators was calculated using a conventional calculation protocol.[2,3] Deferiprone measured 0.04 on the BBB influx efficiency index, indicating a moderate BBB influx efficiency. Four out of the ten 3-hydroxypyridin-4-ones fared better than deferiprone on the BBB influx index. Some chelators failed to cross the BBB. The molecular weight, lipophilicity,

molecular volume and total polar surface area of all 10 chelators did not correlate with their BBB influx efficiency.

Conclusion

Four 3-hydroxypyridin-4-ones with superior BBB influx efficiency than deferiprone have been identified. Structurally, the presence or absence of specific functional groups at the second, fifth and sixth positions of the 3-hydroxypyridin-4-one clearly attributes to the BBB influx efficiency of a chelator. Moreover, the length of the N-alkyl substituent of the 3-hydroxypyridin-4-one plays a dominant role in achieving a high BBB influx efficiency. Neuronal cell culture experiments to evaluate the neuroprotective efficacy of the four selected 3-hydroxypyridin-4-ones will assist in the identification of a prospective lead compound.

References

1. Gaeta A, Hider RC. The crucial role of metal ions in neurodegeneration: the basis for a promising therapeutic strategy. *Br J Pharmacol* 2005; 146: 1041–1059.
2. Preston JE *et al.* Permeability of the developing blood-brain barrier to ^{14}C-mannitol using the rat *in situ* brain perfusion technique. *Brain Res Dev Brain Res*. 1995; 87(1): 69–76.
3. Alexander B *et al*. Hyperammonaemia reduces intracellular 22Na (sodium) ion and extracellular 86Rb ion concentrations in the blood-brain barrier of the rat. *Metab Brain Dis* 2005; 20(1): 19–33.

11
Derivatisable fluorescent framework for calcium detection

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Introduction and Objectives

Fluorescent probes have evolved into an extremely useful tool for the detection of calcium in biological systems. A series of iminocoumarin-based fluorescent Ca^{2+} probes have been synthesised incorporating the Ca^{2+} chelating structure of 1,2-Bis(2-aminophenoxy)ethane-*N*,*N*,*N*′,*N*′-tetraacetic acid (BAPTA). One of them, benzothiazole iminocoumarin (BTIC), uses an iminocoumarin substituted at the 3-position with a benzothiazolyl group. Our objective is to derivatise BTIC to produce fluorophores which can be attached to surfaces (e.g. microarrays), proteins and other macromolecules (e.g. nucleic acid).

Method

It was envisaged that incorporation of a halogen moiety into the benzothiazolyl group would result in a derivatisable probe 3 (Figure 1). The first synthetic target, salicylaldehyde 1, was obtained via a seven-step procedure and then successfully condensed by a Knoevenagel-type reaction with benzothiazole 2 to afford the desired product 3. The structures of the individual products were confirmed by full spectroscopic analysis.

Results and Discussion

Commercially available 2,5-dibenzyloxy-nitrobenzene was transformed to 4-benzyloxy-2-nitrophenol by selective debenzylation in the presence of trifluoroacetic acid. 5-methyl-2-nitrophenol was treated with 1,2-dibromoethane affording 2-(2-bromoethoxy)-4-methyl-1-nitrobenzene. Subsequent coupling reaction between both products gave 4-methyl-1-nitro-2-(2-(2-nitro-4-phenoxyphenoxy)ethoxy) benzene. Hydrogenation of the nitro groups using palladium catalyst generated the amino functionalities, which underwent *N*-esterification in the presence of *t*-butyl bromoacetate and proton sponge. Finally, a Vilsmeier formylation reaction and hydrogenation using 5% acetic acid and palladium as catalyst afforded salicylaldehyde 1. The synthesis of benzothiazole 2 is a one-step cyclisation commencing with commercially available 2-amino-4-chloro-benzenethiol and malonitrile in the presence of acetic acid. Product 3 was obtained in good yield by Knoevenagel-type reaction of benzothiazole 2 with salicylaldehyde 1 in anhydrous methanol and in the presence of piperidine. The synthesis

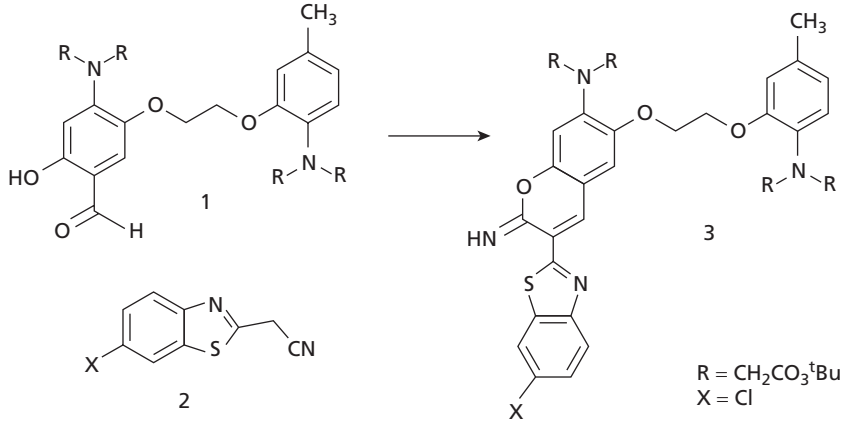

Figure 1 Synthetic route to potential fluorescent probe 3.

of other BTIC derivatives using the versatile precursor 1 with halogenated benzothiazoles (X = Br, I) is currently ongoing.

Conclusion

Deprotection of the tetra *t*-butyl esters would furnish a potential fluorescent probe. The spectral properties and binding affinities for Ca^{2+} would then be determined. In addition, we envisage that further transformation of the halide moiety (X) into an alkynyl group would enable the use of click chemistry to attach the fluorophore to surfaces.

12
Piperidyl indanones as a newer class of anticonvulsants *via* GABAergic pathways: synthesis and preliminary in-vivo evaluation

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Introduction and Objectives

The present series of compounds were synthesised to get synthesise newer anticonvulsant agents that are comparatively more efficacious and safer than the currently used anticonvulsant agents.

Method

A series of new 5,6-dimethoxy-2-{1-[arylamino/alkylamino (thioxo)methyl]-4-piperidyl methyl}-1-indanones (4a-l) were synthesised by the reaction of (2*E*)-5,6-dimethoxy-2-(piperidin-4-yl methyl)-indan-1-one and aryl/alkyl isothiocyanates. Different derivatives were obtained with the modifications at thioamide group (-CSNHR) with substituted aryl and alkyl moieties. All the compounds were characterised by IR, ^{1}H-NMR, ^{13}C-NMR and elemental analyses. The anticonvulsant activity of all the compounds were assessed by maximal electroshock seizure (MES)[1] and chemoshock methods induced with subcutaneous pentylenetetrazole (scPTZ).[2] Neurotoxicity was tested by the Rotorod method.[2] To establish the possible mechanism of action, the most active compounds were evaluated for their effect on 4-aminobutyric acid (GABA) levels in rat brain.[3]

Results and Discussion

All the compounds showed encouraging anticonvulsant activity. Compounds 4d, 4g and 4j were found to be highly active against MES test at a dose of 30 mg/kg at 0.5 h. The compounds 4d and 4j continued the protection at 4 h but at higher dose of 100 mg/kg. In the chemoshock assay, compounds 4a, 4d, 4g and 4l showed activity after 0.5 h of the drug administration at a dose of 100 mg/kg. Among these, compounds 4a, 4d and 4l were also found to be active at 4 h at 300 mg/kg. In the neurotoxicity test, all the compounds except 4b and 4j were found to be less neurotoxic than the standard drug phenytoin. The highly active compounds (4d, 4g and 4j) were subjected to further investigation by estimating the GABA levels in the different regions of rat brain. The statistical data showed that the concentration of GABA increased significantly in the olfactory lobe and the mid-brain region of rat brain after administering the compounds 4d and 4g. Nonsignificant results were obtained with the compound 4j. In the medullary area and cerebellum, compound 4d elevated the GABA concentration significantly, whereas compounds 4g and 4j produced nonsignificant results.

Conclusion

The thioamide derivatives of piperidyl indanone can be regarded as a newer class of anticonvulsant agents with lesser neurotoxicity. Compounds 4d and 4g that were most active in both MES and scPTZ tests were found to elevate the GABA concentration in the rat brain significantly. Thus, the compounds may act by GABA potentiation *via* GABA uptake inhibitory mechanism. Such promising compounds may act as lead molecules for future investigations.

References

1. Swinyard EA *et al.* General principles: experimental selection, quantification, and evaluation of antiepileptic drug. In: Levy RH *et al*. eds. *Antiepileptic Drugs*, 3rd edn. New York: Raven.Press, 1989: 85–102.
2. Kupferberg HJ. Antiepileptic drug development program: a cooperative effort of government and industry. *Epilepsia* 1989; 30S: 51–56.
3. Roberts E. g-Aminobutyric acid. In: Colowick SP, Kap-lan NO eds. *Methods in Enzymology*, vol. VI. New York: Academic Press, 1962: 612.

13
Rapid and efficient isolation of cryptolepine from *Cryptolepis sanguinolenta* using focused microwave extraction methods: a haem-binding antimalarial

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Introduction and Objectives

The aim of this study was to enhance the isolated yield, decrease reaction time and diminish artefact formation

during microwave-induced extraction of the alkaloid cryptolepine from dried roots of *Cryptolepis sanguinolenta* by superheated solvents. This ethanobotanical drug is traditionally used in malaria treatment and glycaemic control of diabetes mellitus. It possesses antimicrobial properties.[1] This study also aimed at replacing conventional, time-consuming Soxhlet extraction using sealed microwave tubes and solvents. Procedures were sought that diminished the risk of solvent ignition and inadvertent exposure to toxic solvents.

Method

A robotic focused microwave system (Explorer, CEM Corporation, Buckingham, UK) was used to heat solvents of increasing dielectric constant (ranging from hexane to trifluoroacetic acid). Cellulose extraction thimbles (10 × 50 mm) were packed with dried, mechanically powdered *C. sanguinolenta* roots (0.1–0.3 g) and held in place with glass wool plugs, and the air was evacuated with argon and then charged with the desired extraction solvent to de-fat the material before alkaloid extraction (e.g. hexane or heptane to extract undesired lipidic material). Extraction of the solid material with concentrated ammonium hydroxide (0.5 ml) and dichloromethane (3 ml) under irradiation (20 min, 150 W) gave a lower alkaloid-rich layer. Alternatively, trifluoroacetic acid and acetic acid allowed direct extraction of alkaloids. The purification of fractions using medium-pressure liquid column chromatography (neutral alumina, 1–40% methanol in chloroform gradient) was further analysed using thin-layer chromatography (chloroform : methanol : c.NH4OH; 79 : 20 : 1; v/v/v). Spots positive to Dragendorff reagent were isolated, and fractions were analysed by spectroscopic methods (UV, IR, mono- and high-field multidimensional NMR (13C-NMR, APT, DEPT, HMBC, HMQC)). Spectrometric methods (positive-ion high-resolution electrospray mass spectrometry) revealed haem binding[2] alkaloid-rich fractions, especially cryptolepine.

Results and Discussion

A variety of polar solvents, especially ethanol in the presence of ammonia, proved highly efficient at extracting the crude alkaloidal material 10–100 times faster than conventional Soxhlet extraction. Using microwaves ensured increased alkaloid extraction by 2–15%, depending on irradiation time. Trifluoroacetic acid proved superior to the acetic acid as an extraction solvent. This method produced cryptolepine with less impurities associated with oxidation and dimerization compared with conventional aerobic Soxhlet extraction. Pure cryptolepine was found to bind strongly to haem (UV), suggesting this as a drug receptor, which is consistent with the mode of action of chloroquine.[2]

Conclusion

Microwave extraction proved safe, convenient and highly efficient. This method may be extended to the isolation of other rare and expensive alkaloids with minimal loss of material and then conveniently analysed for haem binding with UV or high-resolution electrospray mass spectrometry, which shows 1 : 1 stoichiometry with the receptor, as also seen with chloroquine[2,3] and metaquine.[3]

References

1. Sawer IK *et al.* The effect of cryptolepine on the morphology and survival *of Escherichia coli, Candida albicans* and *Saccharomyces cerevisiae. J Appl Bacteriol* 1995; 79(3): 314–321.
2. Dascombe MJ *et al.* Mapping antimalarial pharmacophores as a useful tool for the rapid discovery of drugs effective *in vivo*: design, construction, characterization, and pharmacology of metaquine. *J Med Chem* 2005; 48(17): 5423–5436.
3. Ismail FMD *et al.* Novel aryl-*bis*-quinolines with antimalarial activity *in vivo. J Pharm Pharmacol* 1998; 50(5): 483–492.

14
Synthesis and evaluation of a series of brominated derivatives of 4-hydroxyphenyl ketone-based compounds as potential inhibitors of type 3 17β-hydroxysteroid dehydrogenase

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Introduction and Objectives

We have previously derived the transition-state (TS) of a reaction catalysed by type 3 17β-hydroxysteroid dehydrogenase (17β-HSD3).[1] Using the TS, we designed inhibitors based on the 4-hydroxyphenyl ketone backbone.[2] The structure-activity relationship suggested an interaction between an H-bonding group at the active site and the OH moiety. We concluded that substituents on the phenyl ring that reduce the ability of the inhibitor to undergo H-bonding would result in a decrease in inhibitory activity. Here, we report the results of our study of a range of 3,5-dibromo-4-hydroxyphenyl ketones to test our hypothesis.

Method

The synthesis of the target compounds involved an initial Friedel–Crafts acylation of phenol using a range of alkyl- and cycloalkyl-acid chlorides, followed by the bromination of the intermediate ketone-based compounds to give the desired dibrominated derivatives of 3,5-dibromo-4-hydroxyphenyl ketone. The biochemical evaluation of the synthesised compounds was performed using literature procedure and the microsomes from rat testes and radiolabelled androstenedione as the substrate.[2] The assay was quenched using diethyl ether and the substrate and products were separated using thin layer chromatography, each spot was cut and counted for tritium for 3-min per tube.

Results and Discussion

The reactions proceeded in good yield (typically 60%) and without any major problems; however, the bromination step resulted in the production of by-products that could not be separated, as such, the purification step proved to be troublesome. Consideration of the inhibitory activity shows that the compounds are poor inhibitors of 17β-HSD3; the most potent inhibitor was found to be the nonanoyl derivative, which was found to possess ~35% inhibitory activity against 17β-HSD3 at [I] = 100 μM; the remaining compounds showed low levels of activity with a majority of the compounds lacking inhibitory activity. The two standard compounds, 4-hydroxynonanophenone and 4-hydroxydecanophenone under similar conditions were found to possess approximately 57 and 54% inhibitory activity, respectively. As such, the two bromine atoms at the 3- and 5-positions of the phenyl ring system resulted in a decrease in the binding of the compounds to the active site, thereby leading to a decrease in inhibitory activity, as previously proposed by Olusanjo and Ahmed.[1] The effect of the two bromine substituents could either be the decrease in pKa of the OH moiety or the increase in steric hindrance, leading to a decrease in H-bond formation between the inhibitor and the active site.

Conclusion

The results of this study have added further support to our approximate model of the 17β-HSD3 active site, in particular, the existence of an additional hydrogen bonding moiety which is able to undergo H-bonding interaction with the 4-hydroxy moiety in compounds such as 4-hydroxynonanophenone but is unable to undergo similar interaction in the dibrominated derivatives, thereby resulting in an overall decrease in inhibitory activity.

References

1. Olusanjo MS, Ahmed S. The derivation of a potential transition-state for the reduction reaction catalysed by 17β-hydroxysteroid dehydrogenase type 3 (17β-HSD) – an approximate representation of its active site for use in drug design and discovery *Lett Drug Des Disc* 2007; 4: 527–531.
2. Lota R *et al.* Synthesis and biochemical evaluation of a series of non-steroidal inhibitors of the type 3 isozyme of 17β-hydroxysteroid dehydrogenase (17β-HSD3) *J Steroid Biochem Mol Biol* 2008; 111:128–137.

15
Synthesis and biochemical evaluation of a series of potential novel inhibitors of 17β-hydroxysteroid dehydrogenase

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Introduction and Objectives

The enzyme 17β-hydroxysteroid dehydrogenase (17β-HSD), in particular type 1 (17β-HSD1), is involved in the biosynthesis of the more potent estrogen, namely estradiol, from estrone involving the reduction of the C(17) carbonyl moiety to the C(17) β-OH group. Although the use of aromatase inhibitors has been shown to be useful in the treatment of estrogen-dependent breast cancer, however, as yet, no compounds are in use in the clinic, which inhibit 17β-HSD1. Here, we report our continued efforts[1] to design (and subsequently synthesise) compounds that possess potent inhibitory activity against 17β-HSD1.

Methods

In the synthesis of the inhibitors of 17β-HSD1, we considered our earlier studies on the synthesis of azole-based compounds.[2] The synthesis of the target compounds involved the N-alkylation of imidazole using 2- and 3-brominated derivatives of 1-phenyl-ethanone and 1-phenyl-propan-1-one, anhydrous potassium carbonate and tetrahydrofuran. Biochemical evaluation was undertaken using literature procedure,[3] using rat testicular microsomal homogenate and radiolabeled substrate. After incubation for 20 min, the substrate and products were separated using thin-layer chromatography (TLC). The plate was developed, and the spots were cut out and counted for tritium for 4 min.

Results and Discussion

The synthesis of the compounds did not prove to be troublesome, and the target compounds were synthesised in moderate yield. The compounds were found to be good inhibitors of 17β-HSD in comparison to the two standards used that have been shown to possess potent inhibitory activity,[3] namely 4-hydroxynonanophenone and 4-hydroxydecanophenone, which were found to possess ~57% and ~54% inhibitory activities at [I] = 100 μM, respectively. Under similar conditions, the most potent compounds were found to be 1-biphenyl-4-yl-2-imidazol-1-yl-ethanone and 1-(4-bromo-phenyl)-3-imidazol-1-yl-propan-1-one, which were found to possess 44% and 45% inhibitory activities, respectively. Considering the structure-activity relationship suggests that logP is a factor in the inhibitory process, whilst molecular modelling of these compounds suggests that the imidazole moiety is able to undergo hydrogen bonding with a group at the active site that exists in an area corresponding to the C(15) and C(16) of the natural substrate. Also, modelling of these compounds suggests that the compounds based on 1-phenyl-propan-1-one backbone are able to undergo stronger hydrogen bonding in comparison to the compounds based on the 1-phenyl-ethanone backbone due to the extra CH_2 spacer group which therefore allows the imidazole moiety to approach closer to the hydrogen bonding group at the active site of 17β-HSD.

Conclusion

We have synthesised and evaluated a series of novel inhibitors that would be expected to lower significantly

the level of estrogens (in particular, estradiol) through the inhibition of 17β-HSD1. We also hypothesise that the mode of action of these compounds involves hydrogen bonding to the active site of 17β-HSD1*via* the N atom within the imidazole moiety.

References

1. Lota R *et al.* Synthesis and biochemical evaluation of a series of non-steroidal inhibitors of the type 3 isozyme of 17β-hydroxysteroid dehydrogenase (17β-HSD3). *Lett Drug Des Disc* 2007; 4: 180–184.
2. Owen CP *et al.* Synthesis and biochemical evaluation of a range of potent benzyl imidazole-based compounds as potential inhibitors of the enzyme complex 17alpha-hydroxylase/17,20-lyase (P450 (17alpha)) *Bioorg Med Chem Lett* 2006; 16: 4011–4015.
3. Lota R *et al.* Synthesis, biochemical evaluation and rationalisation of the inhibitory activity of a range of 4-hydroxyphenyl ketones as potent and specific inhibitors of the type 3 of 17β-hydroxysteroid dehydrogenase (17β-HSD3). *J Steroid Biochem Mol Biol* 2008; 111: 128–137.

16
Continued search for potent inhibitors of the cytochrome P-450 enzyme 17α-hydroxylase/17,20-lyase in the treatment of androgen-dependant prostate cancer

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Introduction and Objectives

17α-Hydroxylase/17,20-lyase (P45017α) is under investigation in the treatment of androgen-dependant prostate cancer. We have previously evaluated a series of compounds based upon the benzyl imidazole backbone;[1] however, only a small number of compounds were found to be equipotent to the standard, ketoconazole (KTZ). To increase our library of potent inhibitors of P45017α, we have undertaken the synthesis of a range of (4-alkylphenyl)sulfonate derivatives of 4-hydroxybenzyl imidazole. Here, we report the initial results of our study into the biochemical evaluation of the synthesised compounds as potential inhibitors of P45017α.

Method

In the synthesis of the target compounds, we initially synthesised 4-hydroxybenzyl imidazole (1) using the methodology previously reported by us.[1] The 4-hydroxyphenyl moiety was then derivatised using various (4-alkylphenyl) sulfonyl chlorides and anhydrous dichloromethane as solvent to give the target compounds. The biochemical evaluation of the synthesised compounds (against both the lyase and 17α-hydroxylase components) was undertaken using literature assay procedure using rat testicular homogenate and radiolabelled progesterone and 17α-hydroxyprogesterone for the 17α-hydroxylase and lyase components, respectively.[1] The inhibitors were evaluated at [I] = 100 μM with a substrate concentration of 1.5 μM.

Results and Discussion

The reactions proceeded in good yield (ranging from 40 to 85%), and no major problems were encountered. However, the purification of the potential inhibitors did prove to be troublesome, and a number of purification steps were required. The results of the biochemical evaluation of the compounds against both the hydroxylase and lyase components suggest that the compounds are highly potent inhibitors of P45017α. For example, KTZ was found to possess IC50 values of 206 nm and 2660 nm against lyase and 17α-hydroxylase components, respectively. The weakest inhibitor within the range was found to be the 4-(4-pentylphenyl) sulfonyl benzyl imidazole, with IC50 values of 34 nm and 1040 nm, respectively. Indeed, the most potent compound was found to be approximately 6.8 and 66.5 times more potent than KTZ against lyase and 17α-hydroxylase, respectively. Molecular modelling of these compounds suggests that the sulfonyl moiety is able to undergo interaction with the hydrogen bonding groups at the active site and that there is limited conformational space within the active site, as such, large groups at the 4-position of the phenylsulfonate moiety cannot be accommodated, resulting in a decrease in inhibitory activity.

Conclusion

We have provided novel compounds that have been shown to possess high potent inhibitory activity, which is in the nm range. These compounds show selectivity against the 17α-hydroxylase component, which is therefore beneficial since this would limit side effects of these highly potent inhibitors.

Reference

1. Owen CP *et al.* Synthesis, biochemical evaluation of a range of potent imidazole-based inhibitors of the enzyme complex 17α-hydroxylase/17,20-lyase (P450$_{17\alpha}$). *J Steroid Biochem Mol Biol* 2008; 111: 117–127.

Short Papers in Material Science

17
Sustained release of triclosan from silicone elastomers modified with allyl monomethoxy poly(ethylene glycol)

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