$$pIC_{50} = 0.243(\pm 0.082)chi1\_C - 0.343(\pm 0.052)E\_ang + 0.544(\pm 0.097)a\_don + 13.138$$

$$n = 18, r = 0.928, SE = 0.296, F = 28.731 ICAP < 0.433, Q^2 = 710$$

$$S_{PRESS} = 0.426, S_{DEP} = 0.376, r^2_{bs} = 0.869, S_{bs} = 0.091,$$

$$Chance < 0.001, r^2_{pred} = 0.870 \qquad \text{(Model – 4)}$$

a_don and PEOE_VSA-0 contributed positively, while E_ang contributed negatively to Model-3, wheres chi1_C and a_don contributed positively while E_ang contributed negatively to Model-4. The QSAR analysis gave insight to some common important structural features (i.e. distal end of hydrogen donor groups at nitrogen atom of thiazolidinediones is important for ARI activity and could interact through hydrogen bond formation with the enzyme while the molar refractivity at the phenyl ring of the nucleus plays a significant role in the hydrophobic interaction with enzyme). De-novo analysis inferred that the 3 position of the phenyl ring can be explored for optimization of the analogues.

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052
Fluorescent polymeric binding mimics of CYP2D6

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Studies are described whereby fluorescent molecularly imprinted polymers (MIPs) have been prepared as binding mimics of cytochrome P450 isoform CYP2D6 and which have the potential to form the sensing element in a high-throughput assay for the prediction of CYP2D6 affinity. Most drugs are metabolised by the cytochrome P450 family of enzymes and as a result the half-life of a drug within the body is linked with its rate of cytochrome P450 mediated biotransformation. Some P450s, such as CYP2D6, are subject to population-based polymorphisms and hence it is essential to the drug discovery process to know the P450 metabolic fate of any drug candidate. MIPs are crosslinked polymers containing bespoke functionalised cavities arising from the inclusion of template molecules in the polymerisation mixture and their later extraction. With the inclusion of appropriate functional monomers, binding sites are created, which have a memory for the templates both in terms of shape and matching functionality. Fluorescent MIPs have the added benefit of a fluorophore in their cavities, which may respond to the presence of bound test compound by a change in their fluorescence output (Rathbone & Ge 2001; Rathbone et al 2005). Based upon earlier modelling studies (Islam et al 1991), a series of relatively rigid templates was designed, which potentially represent the "negative" of the CYP2D6 active site. These were incorporated into crosslinked polymers along with a fluorescent functional monomer to give fluorescent MIPs. After extraction of the templates the MIPs were challenged with a panel of drugs to test for any discriminatory recognition of known CYP2D6 binders. Entry of a test compound into an MIP cavity resulted in quenching of the fluorescence of the MIP-bound fluorophore. Calibration studies were also performed using a soluble linear polymer containing the fluorophore to determine the relative quenching abilities of the test compounds towards the fluorophore in a non-MIP environment. The MIPs re-bound their templates and various imprinting effects were encountered for test compound/drug recognition. One MIP in particular exhibited a rational discrimination amongst the related synthetic templates and was reasonably successful in recognising CYP2D6 substrates from a drug panel. The template used to produce this MIP is the subject of ongoing studies to optimise the CYP2D6 substrate recognition profile of the imprinted polymers.

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053
Discovery of a N^1-Benzylidene-pyridine-4-carboxamidrazone with potent and selective activity against Gram-positive bacteria

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Certain N^1-benzylidene-pyridinecarboxamidrazones are known to have antimycobacterial activity and this constitutes most of the published work for these compounds in the antimicrobial area (e.g. Mamolo et al 1993; Billington et al 1998). Most of the published compounds of this type that have been examined for biological activity contain bezylidene moieties substituted with relatively non-polar functionalities (halogen, alkyl, alkoxy) and very little indeed by way of hydrogen bond donor functionality. Therefore, to explore this neglected area of possible bioactivity, we examined a set of phenolic N^1-benzylidene-heteroarylcarboxamidrazones. The compounds were prepared by condensation of the appropriate aldehyde and pyridine-, pyrazine- or quinolyl-heteroarylcarboxamidrazone. The latter building blocks were prepared by the action of ethanolic hydrazine hydrate upon the corresponding cyano compounds. Each compound was initially tested for a zone of inhibition on agar, against both a methicillin-sensitive strain of *Staphylococcus aureus* (reference strain NCTC 6571) and a clinical isolate of MRSA (96-7475). If a zone of inhibition was observed against the MRSA strain, the MIC for that compound was measured against a panel of organisms, using a multi-point innoculator and the agar diffusion method. The panel of Gram-positive organisms used comprised three methicillin-sensitive *S. aureus* strains, 10 MRSA clinical isolate strains, two *E. faecium* strains and seven strains of *E. faecalis* (including six clinical isolates). Eight different Gram-negative bacteria were also tested to investigate the possibility of any broad-spectrum activity. One compound in particular, an N^1-benzylidene-pyridine-4-carboxamidrazone, gave an intriguing and very sharp structure–activity profile. The compound in question contained a phenolic hydroxyl, as well as two bulky lipophilic alkyl, substituents in the benzylidene portion. This compound exhibited the most potent activity of the set against Gram-positive bacteria (MIC 2–4 $\mu g\,mL^{-1}$ against all strains tested). The same high activity (2–4 $\mu g\,mL^{-1}$) was also observed against a panel of seven vancomycin-resistant enterococci clinical strains. Any change made to the substitution pattern in this compound or the deletion or modification of substituents resulted in much reduced or completely abolished antimicrobial activity. Although the compound exhibited no activity against *Mycobacterium fortuitum*, it proved to be highly active against *M. tuberculosis* $H_{37}Rv$ (100% inhibition at 6.25 $\mu g\,mL^{-1}$, Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF), Birmingham, AL). In stark contrast to the Gram-positive results, no activity was observed against any Gram-negative bacteria. It is this dramatic selectivity that is the focus of current investigations.

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054
Synthesis of novel imidazolyl analogues of moclobemide as monoamine oxidase inhibitors

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MAO (EC 1.4.3.4) is an outer mitochondrial membrane FAD containing enzyme found in nearly all tissues. On the basis of their substrate and inhibitor specificities, two major isoforms have been described, the MAO-A and the MAO-B, made up of different polypeptides. MAO-A preferentially catalyses the oxidative deamination of serotonin (5-HT), adrenaline (A) and noradrenaline (NA) and is selectively inhibited by moclobemide or 4-chloro-N-(2-morpholinoethyl)benzamide (Silvestri 2003). The early MAO inhibitors, such as isocarboxazide and tranylcypromine, were nonselective and irreversible. Because of their adverse actions, the therapeutic applications of this first generation MAO inhibitors have been diminished. Today efforts towards the development of monoamine oxidase inhibitors are focused on selective MAO-A or MAO-B inhibitors. Selective MAO-B inhibitors, such as deprenyl, are being examined in the treatment of disorders such as schizophrenia, Alzheimer's disease and Parkinson's disease. The MAO-A inhibitors, such as moclobemide, are effective in the treatment of depression (Hadizadeh & Ghodsi 2005). Our interest in the chemistry of the nitrogen-containing ring, specially imidazole, which provides a site for binding with amino acids within the proteins and enzymes, motivated us to design a similar structure to moclobemide by replacing the moclobemide phenyl ring with substituted imidazole. First, an in-silico study was performed. So, molecules of moclobemide and designed structures were simulated in Hyperchem 7 under semi-empirical method using AM1, closed shell gradient 0.01. Superposing the molecules, not surprisingly, showed high similarity (RMS 0.46 Å) between the molecules, which suggests similar interaction in the active site of MAO. Then novel 1-benzyl-2-(alkylthio)-N-(2-morpholinoethyl)-1H-imidazole-5-carboxamides were synthesized. Initially, a mixture of benzylamine hydrochloride,

dihydroxyacetone dimmer and potassium thiocyanate in n-butanol and glacial acetic acid was stirred for 3 days. After that a precipitate was formed and filtered to give 1-benzyl-2-mercapto-imidazole-5-methanol (1). Then it was reacted with alkyl halide (RX) in alcoholic solution of sodium hydroxide to give 2-alkylthio-1-benzylimidazole-5-methanol (2). Compound 2 was refluxed in chloroform overnight at the presence of manganese dioxide to give 2-alkylthio-1-benzylimidazole-5-carbaldeyde (3). Further oxidation of 3 with aqueous alkaline solution of silver nitrate (tollens reagent) afforded 2-alkylthio-1-benzylimidazole-5-carboxylic acid (5). Compound 5 was reacted with thionyl chloride to give the corresponding 2-alkylthio-1-benzylimidazole-5-carbonyl chloride (6). Condensation of 6 with 2-morpholinoethylamine in tetrahydrofuran at the presence of pyridine gave the title 1-benzyl-2-(alkylthio)-N-(2-morpholinoethyl)-1H-imidazole-5-carboxamides (7). The title compounds and intermediates were characterized by ^{1}H NMR and IR spectroscopy.

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055
Prediction of chemical carcinogenicity based on an evaluated chemical safety database CAESAR

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Numerous chemical substances of natural and synthetic origin have been produced for our use such as various drugs, foods, personal care products, household cleaners, and agricultural chemicals. However, the adverse effects of most of those agents on human health and global environment are not known. Among chemicals currently in commerce, quite a few are ascertained on their safety, and reliable data on chemical hazard assessment are quite limited. Therefore, an attempt on a basis of Quantitative Structure–Activity Relationship (QSAR) models for estimating carcinogenicity has been performed (Tanabe & Matsumoto 2002; Romualdo 2003; Tanabe et al 2004). To construct a database system having reliable data on chemical toxicity, a CAESAR (Computer-aided Evaluation of Chemical Safety with QSAR) system has been developed in this work. It consists of two databases. One contains reliable, critically reviewed, experimental hazard data on selected chemicals. For example, carcinogenicity data on about 1000 chemical substances have been collected from various sources, such as NTP, NCI and others, and ranked into five categories according to the reliability of the risk of incidence of cancer. Another contains hazard data predicted from QSAR models, which relate toxicity of molecules to chemical structure on the basis of available biological properties of more than 100 000 chemical substances in commerce. This system predicts chemical carcinogenesis by the artificial neural network (ANN) with back-propagation method. For the ANN modelling, a three-layered neural network model to predict the carcinogenicity of a variety of compounds was developed. For the output, the data of 454 compounds with the carcinogenic activity of male rats from the database were employed. The ANN was used to classify the chemicals studied into two categories, namely inactive or active. The set of 454 compounds was split into training (144 compounds), validation (143) and test (167) sets. The carcinogenicity data were entered into the output layer (0 for noncarcinogenic or 1 for carcinogenic chemicals). The inputs were 10 principal components from 37 kinds of molecular descriptors, including quantum chemical descriptors. To solve the problems, such as over-training, over-fitting and local minimum in training, the neural network with the error-back-propagation algorithm, various conditions of the network such as the training cycles and neuron numbers of the intermediate layer were optimized. While an NN was trained by using the learning set, the errors between the output and teaching data for the learning, validation and test sets were counted in each cycle. The optimum model showed a correct classification rate close to 74%, which is higher than any reported values in the Predictive Toxicology Challenge 2000–2001 contestants (www.informatik.uni-freiburg.de/~ml/ptc/). The present result demonstrated the superiority of the ANN as a nonlinear modelling method, such as multiple linear regression.

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056
Dipeptidyl peptidase IV deficiencies are associated with low relative abundance of nitrergic cells in the thymus of sub-strains of Fischer F344 rat

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Dipeptidyl peptidase IV (Dpp4) activity of CD26 is associated with the co-activation of T-cells alongside T-cell receptor mediated stimulation. Pharmacological inhibitors of Dpp4 offer a therapeutic possibility in the suppression of autoimmune activity of peripheral T-cells (Mathisen 2003). However, the same signalling mechanism, through T-cell receptor and co-stimulatory molecules, such as Dpp4/CD26, may underlie central (thymic) tolerance by clonal deletion of potentially autoreactive cells. The abundance of cells expressing inducible nitric oxide synthase (iNOS) coined nitrergic, is proposed as one mechanism involved in the negative selection of self-reactive thymocytes. Nitrergic cells are deficient in autoimmune-susceptible Lewis rat compared with resistant Fischer and Sprague Dawley strains (Downing et al 1998). Genetic or pharmacological disruption of T-cell co-stimulation within the thymus may also lead to reduced nitergic cell activation in thymus. We examined nitrergic cell abundance in two sub-strains of the F344 Fischer rat (GER and JAP) characterised for inactivity of Dpp4 compared with wild type (USA) (Karl et al 2003). All rats were subject to prior periodontal treatment, females and aged (~22 months) with JAP and GER being 9 and 14 days younger than USA, respectively. It was hypothesised that either or both inactive Dpp4$^-$ mutant sub-strains of F344 Fischer rat, GER and JAP, would have reduced co-activatory signalling; this would lead to reduced nitergic cell activation in thymus compared with wild type (Dpp4$^+$) USA. Paraformaldehyde-fixed thymi were stored frozen (−20°C) before parallel processing of batches containing all three strains for enzyme histochemistry in 100-micron sections (four sections from four rats per strain). Abundance of medullary nitrergic cells (mean count/mm^2 ± s.e.m.) stained positive by NADPH-diaphorase was used as a marker of inducible nitric oxide synthase (iNOS). Counts and section surface area measurements were made from glycerol-mounted sections. Results confirmed lower abundance of nitrergic cells in both JAP (2.27 ± 0.29) and GER (1.92 ± 0.32) thymus compared with the USA sub-strain (6.88 ± 0.84; one way analysis of variance $P < 0.001$). There was no significant difference between nitrergic cell abundance of the Dpp4$^-$ sub-stains (GER and JAP) according to Tukey's follow up test. Our results are consistent with the notion that Dpp4 activity of CD26 contributes to co-stimulatory function during central thymic tolerance via the expression of iNOS. Although JAP and GER Dpp4$^-$ sub-strains may have an increased risk of autoimmune T-cell repertoires, these cells may be deficient in their ability to activate. The use of inhibitors of Dpp4 to treat multiple sclerosis should be monitored for their ability to cause autoimmune complications following withdrawal, as has been reported for cyclosporine A (Kosaka et al 1990).

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057
Structural properties of andrographolide derivatives with anti-cancer activity

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Andrographolide (A), a labdane diterpenoid from *Andrographis paniculata*, is cytotoxic against cancer cells but has additional activity (e.g. hypotensive and anti-inflammatory). To eliminate side-effects it is desirable to define the structural features that endow A with one particular type of activity. Nanduri et al (2004) prepared an epoxy derivative of A and investigated the effect on cytotoxic activity of making acetyl or larger esters out of one or more of its three hydroxyl groups. Surprisingly, mono- and diacetylation reduce activity but triacetylation enhances it. By determining the crystal structure of triacetylandrographolide (TAA) and comparing it with the similarly acetylated epox-