What kind of chemical structure will help the control of the most life-threatening side effects associated with CoVid-19- Some Salicylamide derivatives appears to be able to compete.

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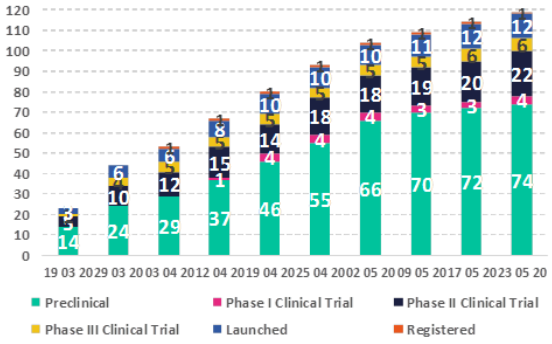
SEQENS Scientific Director

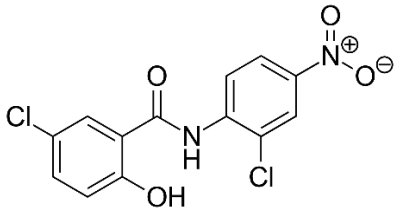
Due to the urgency of finding a treatment against CoVid-19, an increasing number of synthetic small molecules were involved in pre-clinical and clinical trials to find (a) potential drug candidate(s) against CoVid-19.

Mid-May, more than 100 molecules were subjected to trials: some are already approved drugs being re-evaluated in view to repositioning them, while others are still in the clinical phase for their initial indication. Different therapeutic strategies are being considered.

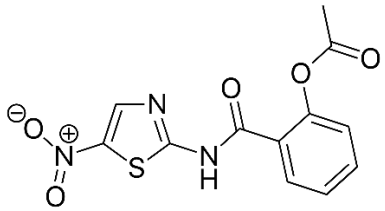


Some of these small molecules - called antivirals - aim to prevent the virus from entering host cells or replication by acting as protease or polymerase inhibitors, in order to block contamination and spread of the virus in the organism. Several candidates initially developed to address other diseases as ....viruses such as Influenza, Hepatitis, HIV, Ebola, Malaria, SARS or MERS, have been submitted for study.

Niclosamide is inhibiting replication of the coronaviruses and **Nitazoxamide** ('Alinia' from ROMARK Labs) is blocking 'Viral translation' and globally boosting the Immune system. Both compounds are among the molecules tested initially as phosphodiesterase's inhibitors...

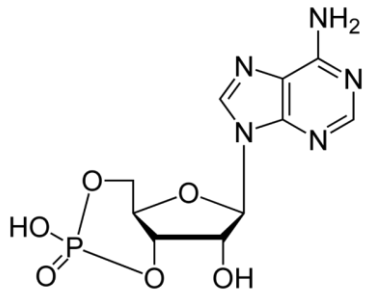


NICLOSAMIDE

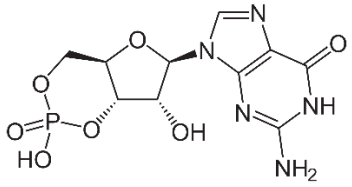


NITAZOXAMIDE

The class of phosphodiesterases is divided into 11 sub-classes and each of them have a biological role. Phosphodiesterases are notably studied for their specific action in the control of the well-known 'second messengers': **c-AMP & c-GMP** inducing a response in the cells. The biologic effects induced by these cyclic nucleotides are regulated by two classes of organic enzymes: **Adenylate Cyclase** that promote the formation of **c-AMP & c-GMP** from ATP and **Phosphodiesterases** (PDE) that can stop their actions by respectively transforming these cyclic nucleotides back to their open-form 5'-nucleotide.



c-AMP



c-GMP

It is possible that a biological cascade takes place as c-AMP can activate different type of protein kinases, enzymes known to promote the transfer of a 'Phosphoryl function ' on an 'Hydroxyl Group' of a protein… (namely on Serine, Threonine and Tyrosine amino-acid residues available on the protein). When 'Phosphorylated', the structure of these proteins are modified and they become active, playing different and important roles inside the cell. (i.e.Tyrosine Kinases inhibitors play a strong role in cancer control and have led to the well-known class of the '-TINIB'-drugs)

If we consider the respective chemical structure of both NICLOSAMIDE & NITAZOXAMIDE (see the respective chemical structure). Both of them are bearing a **'Salicylamide'** core structure, characterized by a phenyl group substituted at least by a carboxamide function next to a hydroxyl (or acetoxy group) and it is already known that a number of these derivatives are phosphodiesterases inhibitors especially for the sub class PDE4. As briefly explained above, PDE ended the biochemical effect of the c-AMP by performing ring-opening of the nucleotide second messenger in the cells. Finally, a complex organization of the PDE-genes, is able to control the second messenger level and also to fine-tune the signaling channels. Then blockage of the PDE means a high level of **c-AMP & c-GMP** that induced multiple cellular effects i.e.:

-Smooth muscle relaxation of the respiratory tract

-Inhibition of cellular inflammation

-Immune response's level

Indeed, PDE4 inhibitors are in the front line to limit the complications due to the development of CoVid-19. Especially in affected patients where excessive inflammatory response is observed associated with the release of an excess of protein, interleukin-6, which suractivates the immune response.

Typical PDE4 inhibitors examples available as a Drug substance today are:

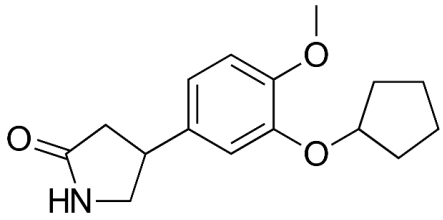
ROLIPRAM & **ROFLUMILAST**

It should be mentioned that each sub-class of PDE, as PED4 has been again divided in sub-sub-classes, with the associated typical physiological effects:

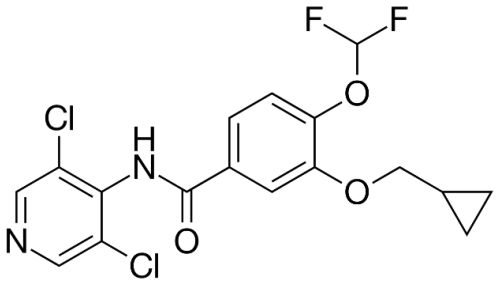
i.e. -PDE4A & PDE4D inhibition with antidepressants effect

i.e. -PDE4B inhibition with antipsychotic effects

i.e. -PDE4C inhibition with anti-inflammatory effects



ROLIPRAM



ROFLUMILAST

SEQENS is the world leader and unique Western player on the Salicylic Acid market. Its c-GMP production site in France benefits from a favorable vertical integration and robust access to the raw material, being located next to the phenol production unit on the Roussillon chemical platform. That advantage allows SEQENS to have strong position as Acetyl Salicylic Acid (Aspirin) producer, and to be able to contribute to this very specific field of 'Salicylamides' in order to complement the other

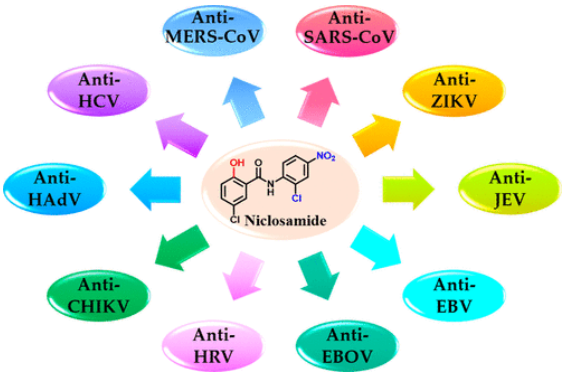
'weapon-molecules' against the effects induced by CoVid'19 contamination.

A quick survey of SciFinder Database based on structural investigation around 'Salicylamide' core, leads to about 5000 molecules cited between 2010 & 2020. Obviously with all the possible variations around 'aromatic atom substitution' and also being part of more complex molecules.

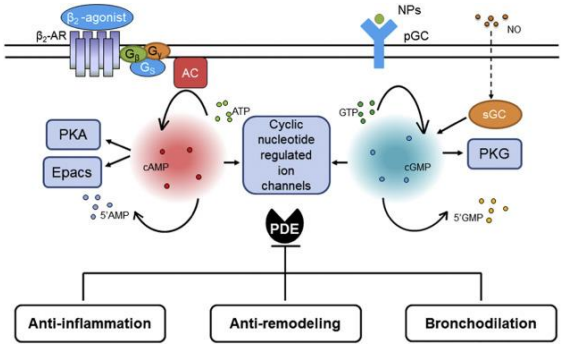
If we looked at the Patent around these Salicylamides derivatives, most of the big pharmaceuticals companies have explored these kinds of products. If we restricted the question to 'Chiral Phenethyl amines' coupled with Salicylic Acid, there is still more than 400 structures mentioned...

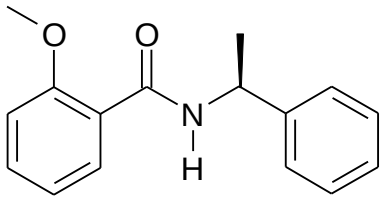
SEQENS as a provider of Drug Substance has a portfolio of 'Proprietary Molecules' with around 40 A.P.I.'s. An important key starting material for one of these A.P.I.'s (CINACALCET) is *R*-Naphthyl Ethyl Amine (*R*-N.E.A.). It appears that when Acetyl Salicylic Acid is coupled with *R*-NEA, the corresponding Salicylamide derivative has been already tested against 'Severe Acute Respiratory Syndrome Coronavirus papaïne like protease'. (See J.Med.Chem. 2009, N°52 Issue 16, pp.5228-40; Purdue University)

Finally, this kind of molecule can be the first example of what can be seen as a wide-range anti-viral series.



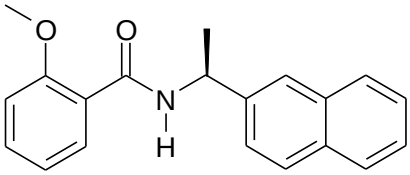
As it has been described in this short paper, where we have tried to explain what is the rationale to check 'Salicylamide structures', this approach represents only the small part of SEQENS effort for its commitment to deliver 'Essential Drug Substances'. The C.D.M.O. part of the company was also strongly involved in many other supply chains regarding a number of synthetic targets designed to cope with CoVid'19 pandemic.





SALICYLAMIDE Derivative, obtained by reacting chiral Phenethyl amine (R-P.E.A.) & 2-Methoxy-Benzoïc Acid

(by analogy with the structure below already tested)



SALICYLAMIDE Derivative, obtained by reacting chiral Naphthyl ethyl amine (*R*-N.E.A.) & 2-Methoxy-Benzoïc Acid.

(tested against SRAS-Coronavirus see J.Med.Chem. 2009, N°52, Issue 16 pp. 5228-40)