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SYNTHESES OF NEW TXA_2/PGH_2-RECEPTOR ANTAGONISTS AND THEIR BIOLOGICAL PROPERTIES

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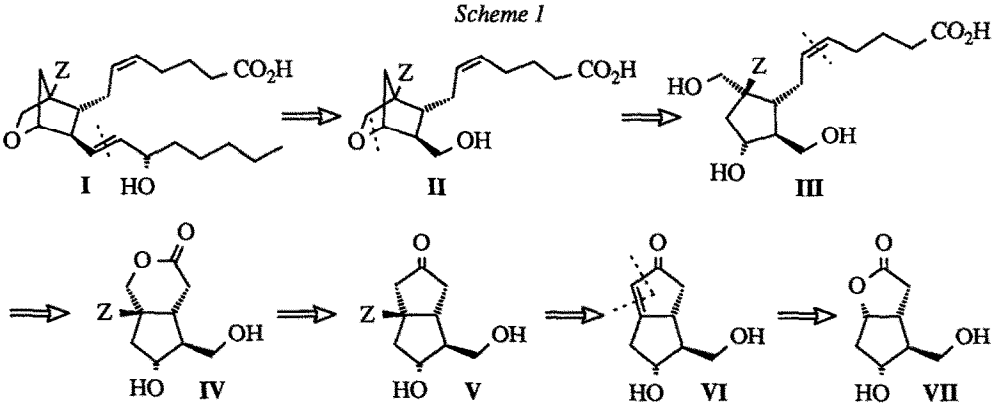
SUMMARY: The syntheses of new types of TXA_2/PGH_2-receptor antagonists and some structure activity relationships are discussed. It is shown that a suitable substituent attached directly to the carbon bridge of the 2-oxabicyclo[2.2.1]heptane system of the standard TXA_2/PGH_2-receptor agonist U 46619 changes the biological profile from an agonist to an antagonist and results in biologically very active compounds.

INTRODUCTION AND CONCEPT: Thromboxane A_2 (TXA_2) and Prostaglandin H_2 (PGH_2) are produced in vivo from arachidonic acid via the 11-cyclooxygenase pathway[1]. Both compounds are potent stimulators of platelet aggregation, induce contraction of vascular and airways smooth muscle, and are considered to interact with the same cell-surface receptor or receptor-type[2]. Because of the association of TXA_2/PGH_2 with a number of pathological states[3], e.g., myocardial ischemia, coronary vasospasm, asthma, and hepatorenal diseases, the intensive search for specific TXA_2/PGH_2-receptor antagonists led to the synthesis of a variety of prostanoid (e.g. SQ 29548, BMS-180291, S-145, Ono-8809, ICI-192605, GR-32191, EP 092) and non-prostanoid structures (e.g. BM 13177, 13505, Bay-u-3405, L670596)[4].
In one of our own approaches, we tried to change the agonist profile of the stable TXA_2/PGH_2-mimic U 46619[5] (**I**, Z=H, *Scheme 1*) adding a residue Z to the carbon bridge of the bicyclic ring system to obtain compounds with antagonist properties. Our synthetic strategy is outlined in the retrosynthetic analysis (*Scheme 1*).

Scheme 1

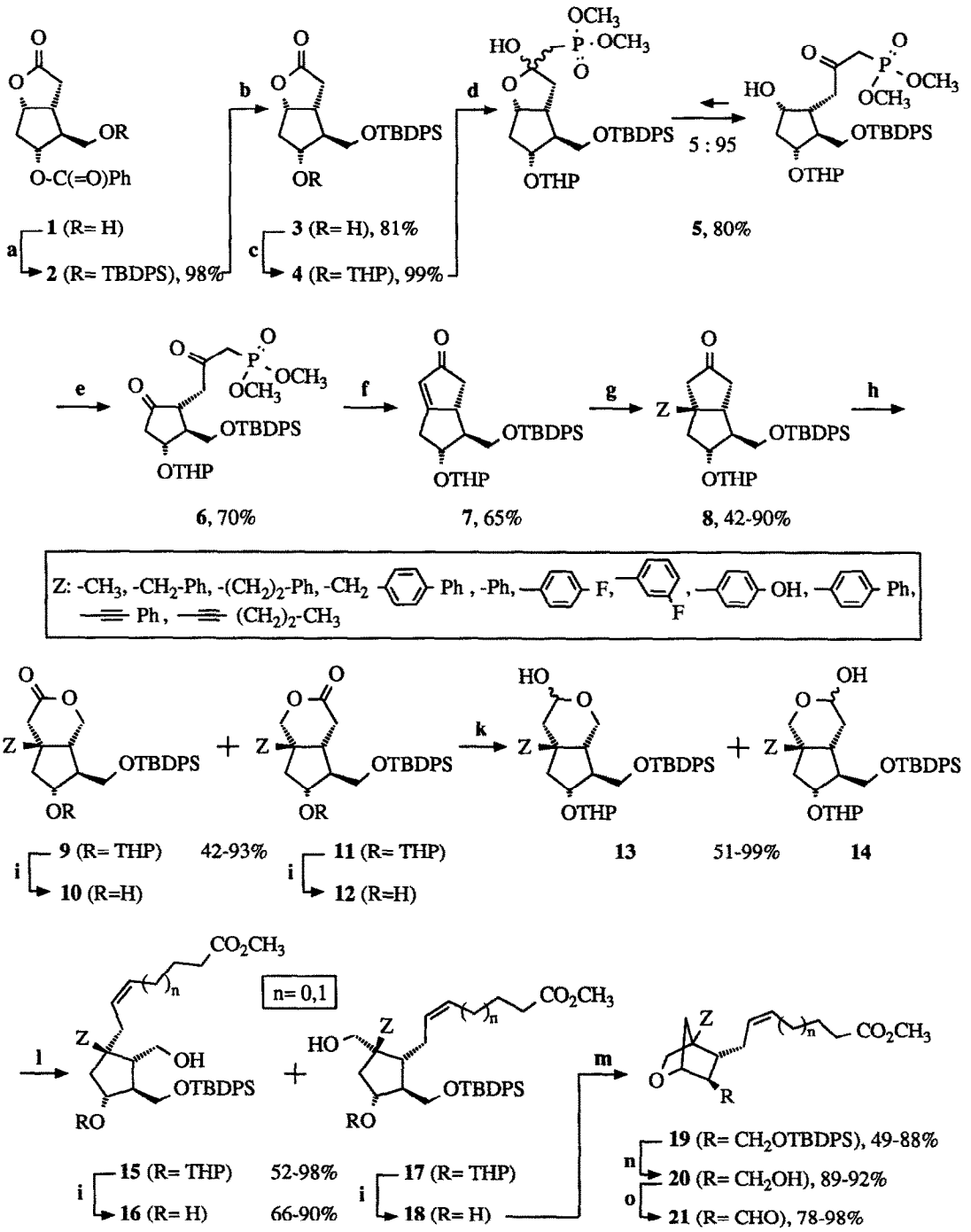


Removal of the ω-chain in **I** and opening of the cyclic ether moiety leads to the prostanoid precursor **III**. Cleavage of the double bond results in the Baeyer-Villiger product derived from ketone **V**, in which the residue Z is introduced by 1,4-addition to the key intermediate **VI**. **VI** finally can be prepared regioselectively from Corey-lactone **VII**, which is available in both enantiomeric forms.

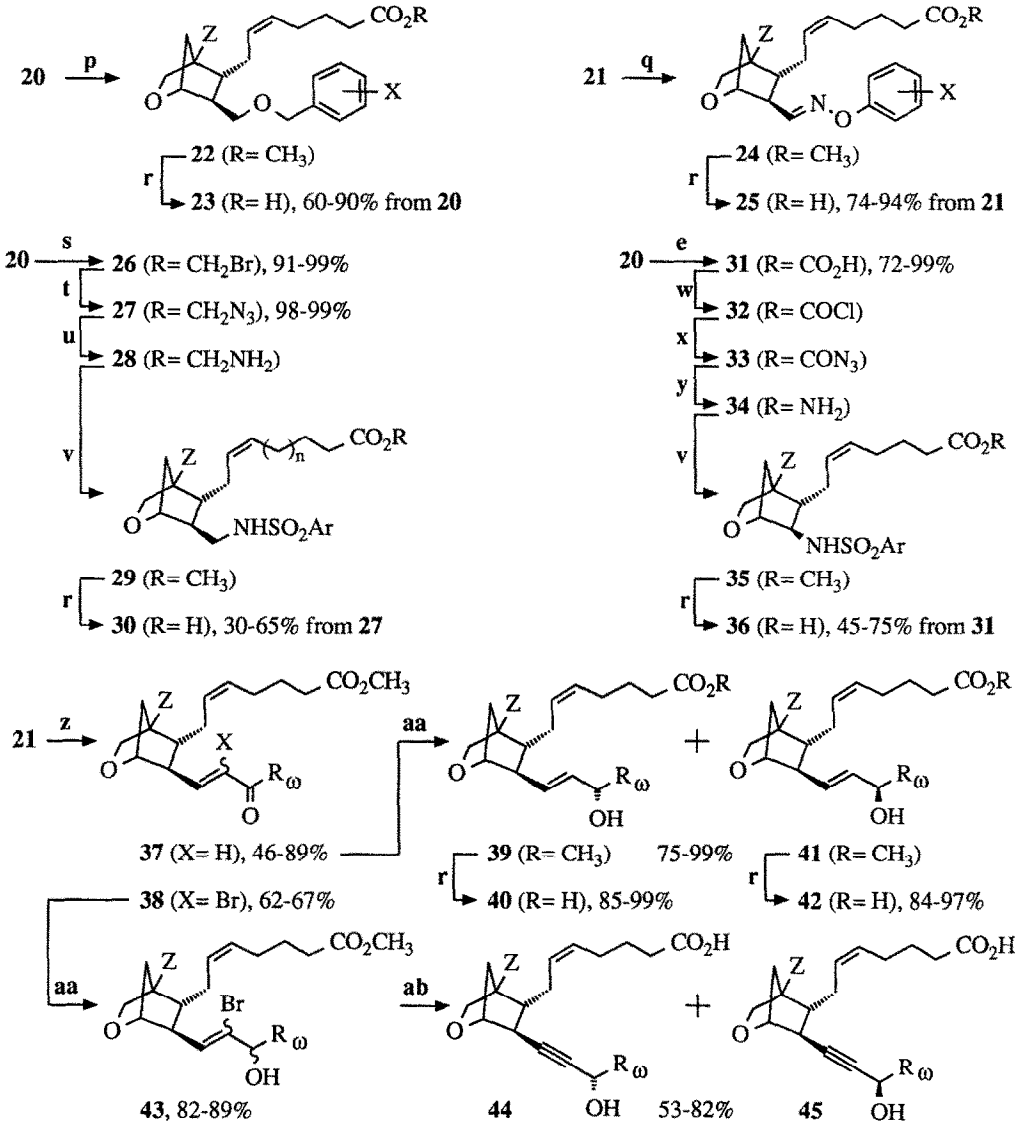
SYNTHESIS: The synthesis started from (+)- as well as (-)- Corey-lactone **1**, although it is shown here for (-)-**1** with the correct absolute configuration of the natural prostanoids (*Scheme 2*). The hydroxy groups were protected as tert.-butyldiphenylsilyl (TBDPS) and tetrahydropyranoyl (THP) ether, respectively, by standard methods. The formal exchange of the lactone oxygen by a carbon atom was achieved in a three step sequence according to P.A. Aristoff et al.[6] by addition of deprotonated dimethyl methylphosphonate, Jones-oxydation to 1,4-diketone **6** and cyclisation to the key intermediate **7**. The residue Z was introduced either by Cu(I) catalyzed 1,4-addition of Grignard-reagents when Z represents an alkyl or aryl group, or by Ni(I) catalyzed 1,4-addition of diethylaluminum alkynes in the cases were Z is a terminal alkyne[7]. Baeyer-Villiger oxidation gave a nearly 1:1 mixture of regioisomers **9** and **11**, which could be separated by chromatography on silica gel after reduction to the lactols **13** and **14**. Reoxidation to the corresponding lactones **9** or **11** and removal of the THP-ether gave compounds **10** and **12** in which the regioisomers could be readily assigned based on the coupling pattern (AB versus ABX) of the methylene protons adjacent to the lactone oxygen in the ^{1}H-NMR spectrum. The introduction of the α-chain into **13** and **14** by Wittig-reaction, formation of the methyl ester and selective cleavage of the THP-ether led to the 1,4-diols **16** and **18**. Although the separation of the regioisomers could be performed much more readily with diols **16** and **18** independent of the nature of Z, Mitsunobu cyclisation[8] of this mixture yielded only the desired ether **19**, while **16** gave mainly other, not identified products. Alcohol **20**, obtained after removal of the silyl group, is the key intermediate for the introduction of various ω-chains. As indicated in *Scheme 3*, the alcohol was directly transformed into benzylic ethers (**23**), sulfonamides (**30**, **36**), or -after oxidation to the aldehyde **21**- into oxime ethers (**25**) or prostanoid chains via Wittig-Horner reaction. After in situ bromination of deprotonated phosphonate with NBS, the resulting vinyl bromide **38** was reduced to give then on HBr elimination the 13,14-triple bond. The epimeric alcohols were readily separated by chromatography on silica gel. Their configuration at C-15 was assigned on the assumption that the more active epimers possess the same 15α-configuration of the hydroxyl group as the natural prostaglandins.

RESULTS: The selected compounds listed in *Tables 1* to *4* allow some general statements for structure-activity relationships in this structural class. As depicted in *Table 1*, the TXA_2-agonist properties for the parent compound U 46619 (entry 1b) can be converted into TXA_2-antagonist properties if Z is larger than methyl. Furthermore, on inverting the absolute configuration as shown in *Table 2* for different types of ω-chains and some selected groups Z, the affinity to the TXA_2/PGH_2-receptor is improved significantly. The effect of the substitution pattern for Z=phenyl on the receptor binding for different types of ω-chains is given in *Table 3*. Compounds with Z=biphenyl and sulfonamides as ω-chains show the strongest binding. The introduction of an additional methylene group between the bicyclic ring system and the sulfonamide nitrogen has no significant influence on the receptor binding (entries 8, *Table 3* and 9, *Table 4*), but the ability to inhibit platelet aggregation, however, is enhanced 10-fold. *Table 4* shows the influence of the length of the α-chain as well as the double bond on receptor binding for different substituted aryl sulfonamides. It is obvious that a double bond is not necessary and that the shortening of the α-chain by one methylene group is well tolerated and in some cases even improves receptor affinity. All derivatives listed in *Table 4* are pure TXA_2/PGH_2-antagonists. For example, compound of entry 3 is 100-fold more active in inhibiting the aggregation of washed human platelets than the standard TXA_2-antagonist SQ 29548.

Scheme 2


1 (R= H)
2 (R= TBDPS), 98%
3 (R= H), 81%
4 (R= THP), 99%
5 : 95
5, 80%
6, 70%
7, 65%
8, 42-90%
Z: -CH3, -CH2-Ph, -(CH2)2-Ph, -CH2 Ph , -Ph, F, OH, Ph, Ph, (CH2)2-CH3
9 (R= THP) 42-93%
10 (R=H)
11 (R= THP)
12 (R=H)
13 51-99%
14
n= 0,1
15 (R= THP) 52-98%
16 (R= H) 66-90%
17 (R= THP)
18 (R= H)
19 (R= CH2OTBDPS), 49-88%
20 (R= CH2OH), 89-92%
21 (R= CHO), 78-98%

Scheme 3

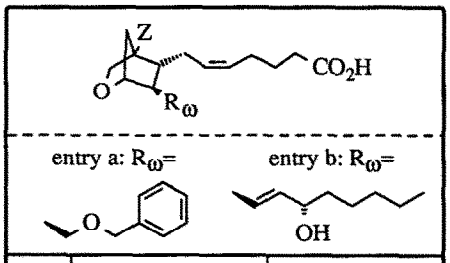


CONDITIONS: a: TBDPS-Cl, imidazole, DMF, 23°C, 2h, argon; **b:** K_2CO_3, MeOH, 23°C, 16h, argon, SiO_2; **c:** dihydropyrane, cat. p-TsOH, CH_2Cl_2, 23°C, 1h, argon, SiO_2; **d:** dimethyl methylphosphonate, n-BuLi, THF, -78°C, 1.5h, argon, SiO_2; **e:** Jones-oxidation **f:** K_2CO_3, 18-crown-6, toluene, 23°C, 16h, argon, SiO_2; **g:** Z-Mg-X, cat. CuOAc, ether, -15°C, 0.5-3h or Z-$AlEt_2$, cat. Ni(I), ether, -10°C, argon, SiO_2; **h:** m-CPBA, $NaHCO_3$, CH_2Cl_2, 23°C, 10-18h, argon, SiO_2; **i:** cat. PPTs, EtOH, 55°C, 2-7h, argon, SiO_2; **k:** DIBAL, toluene, -70°C, 0.5-1h, argon; **l:** n-BuLi, HMDS, carboxybutyltriphenylphosphonium bromide (n=1) or carboxypropyltriphenylphosphonium bromide (n=0) , THF, 30-60°C, 2-6h; CH_2N_2, ether, CH_2Cl_2, 5°C, 0.5-2h, argon, SiO_2; **m:** PPh_3, DEAD, toluene, 50-60°C, 3-20h, argon, SiO_2; **n:** 1M TBAF, THF, 23°C,

1-4h, argon, SiO_2; **o:** Swern-oxidation; **p:** Hal-CH_2-C_6H_4-X, 50% KOH, cat. Bu_4NHSO_4, 23°C, 16h, argon, SiO_2; **q:** H_2N-O-C_6H_4-X, EtOH, cat. pyridine, 50°C, 2-3h, argon, SiO_2; **r:** 5% LiOH, MeOH, 23°C, 5-16h, argon, SiO_2; **s:** CBr_4, Ph_3P, collidine, acetonitrile, 23°C, 16h, argon, SiO_2; **t:** NaN_3, DMF, 60°C, 2-4h, SiO_2; **u:** Ph_3P, THF, 23°C, 16h, H_2O, rf, 1h; **v:** $ClSO_2Ar$, CH_2Cl_2 23°C, 0.5h, argon, SiO_2; **w:** $SOCl_2$, CH_2Cl_2, 5-23°C, 6h, argon; **x:** NaN_3, H_2O, CH_2Cl_2, cat. Bu_4NHSO_4, 5°C, 1h, argon; **y:** F_3CCO_2H, H_2O, CH_2Cl_2, 50°C, 4h, argon, SiO_2; **z:** NaH, phosphonate, (NBS), DME, or LiCl, phosphonate, DBU, acetonitrile, 23°C, 3-23h, argon, SiO_2; **aa:** $NaBH_4$, MeOH, -40°C, 1h, argon, SiO_2; **ab:** KO-t-Bu, DMSO, THF, 23°C, 2-4h, argon, SiO_2.

Table 1

Influence of group Z on receptor affinity and TXA_2-agonist/antagonist properties



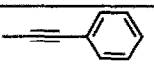
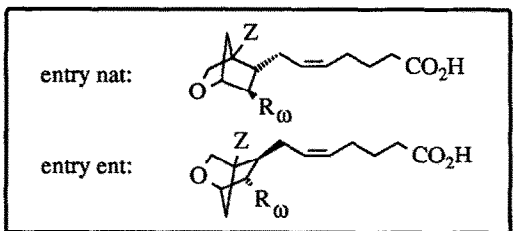
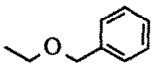
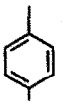
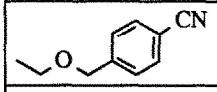
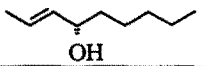
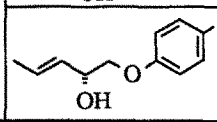
Entry	-Z	C_F (TXA_2)* and Quality**
1a 1b	-H (U 46619)	>>1000 ? 36 ago
2a 2b	$-CH_3$	>1000 ? 320 ago
3a		300 ant
4a 4b	$-CH_2$ 	300np ant 250 ant
5a	$-CH_2$  Ph	800 ant
6a 6b	$-(CH_2)_2$ 	750 ant 420 ant
7a	 $(CH_2)_2CH_3$	90 ant
8a		30 ant

Table 2

Influence of absolute configuration on receptor affinity and TXA_2-agonist/antagonist properties

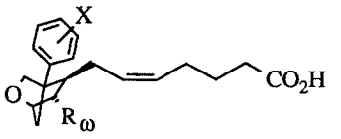


Entry	-Z	-R_ω	C_F (TXA_2) and Quality
1-nat 1-ent	-Ph		300 ant 60 ant
2-nat 2-ent	-≡-Ph		30 ant 12 ant
3-nat 3-ent	 F		125 ant 60 ant
4-nat 4-ent		 CN O	900 ? 6 pa
5-nat 5-ent		 OH	650 ? 25 ant
6-nat 6-ent		 F O OH	375 ant 2 pa

The TXA_2/PGH_2-receptor affinities are given as competition factor C_F= (ID_{50}-test)/(ID_{50}-standard); SQ 29548 is used as standard TXA_2/PGH_2-receptor antagonist; np means not parallel.

The quality of compounds binding to the TXA_2/PGH_2-receptor is defined as follows: antagonists are able to inhibit the aggregation of (human) platelets as well as the contraction of rabbit aorta induced by the standard TXA_2/PGH_2-agonist U 46619 ($1 \cdot 10^{-6}$M); partial agonists either amplify ADP induced platelet aggregation and/or contract rabbit aorta but still inhibit platelet aggregation induced by U 46619; agonists aggregate platelets and/or contract the rabbit aorta by their own.

Table 3:
Influence of phenyl substitution on receptor affinity and TXA_2-agonist/antagonist properties



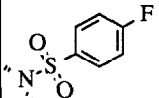
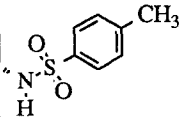
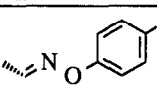
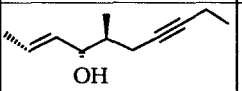
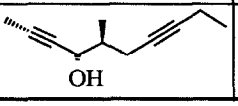
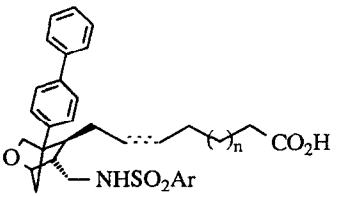
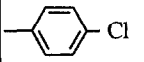
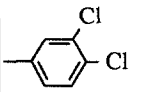
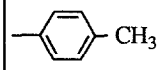
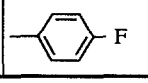
Entry	X	-R_ω	C_F (TXA_2) and Quality
1	3-F		250 ant
2	4-F		120 ant
3	4-OH		30 ant
4	4-Ph		2np ant
5	3-F		120 ant
6	4-F		170np ant
7	4-OH		520 ant
8	4-Ph		2np ant
9	3-F		10 ant
10	4-F		16 ant
11	4-Ph		16np ant
12	4-F		26 ant
13	4-Ph		20np pa
14	4-F		4 ago
15	4-Ph		12np pa

Table 4:
Influence of double bond and α-chain length on receptor affinity of TXA_2-antagonists



Entry	n	Δ	-Ar	C_F (TXA_2)
1	1	Z		0.4 np
2	1	sat		1.4
3	0	Z		0.1 np
4	0	sat		0.3 np
5	1	Z		4.2 np
6	1	sat		12.0
7	0	Z		6.0 np
8	0	sat		5.0
9	1	Z		4.0 np
10	0	Z		0.05
11	0	sat		0.1
12	0	Z		0.05
13	0	sat		0.1

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